Gabapentinoid prescriptions in patients with osteoarthritis: an analysis of data from the Clinical Practice Research Datalink

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Declaration

The idea for this project, completed for my Master of Philosophy (MPhil), was devised by Professor George Peat. Working as principal investigator, and assisted by my other supervisors Drs Julie Ashworth, John Bedson and Dahai Yu, Professor Peat completed a large proportion of the Independent Scientific Advisory Committee (ISAC) protocol for use of the CPRD. Whilst I did contribute to this form, particularly regarding the study outcomes and background, much of this work was completed very early in my research project and sections of this form, such as sample size calculations, were not carried out by myself. I did however draft the responses to the feedback we received on the ISAC protocol in March 2018, and comments were provided by my supervisors prior to responding.

Professor George Peat, as well as Dr Ashworth, Dr Bedson, and Dr Ross Wilkie provided valuable comments on my drafted work, although all concepts presented in this thesis are mine. Dr Dahai Yu prepared and cleaned the CPRD datasets for me to analyse, and did assist with the person-time denominator used in the incidence analyses. However the presentation, interpretation and discussion of all findings in this thesis are my own work.

Abstract

Amid a substantial rise in gabapentin and pregabalin (gabapentinoid) prescribing and increasing concerns with their potential for misuse and diversion, there are anecdotal reports of their use for osteoarthritis. The aim of my thesis was to understand whether osteoarthritis may have contributed to the general rise in the use of the gabapentinoids.

A series of scoping literature reviews summarised the context and potential rationale for the off-label use of gabapentinoids for osteoarthritis. An original analysis of data from the Clinical Practice Research Datalink (CPRD) was then undertaken.

383,680 patients aged over 40 years with a new diagnosis of osteoarthritis recorded between 1995 and 2015 were identified and followed for a median of 5.1 years to their first gabapentinoid prescription or other censoring event. 35,031 (9.1%) cohort members received a gabapentinoid prescription. The crude incidence rate of first gabapentinoid prescription among this cohort of osteoarthritis patients increased from 1.71 (95% CI: 1.37, 2.11) per 1,000 person-years in 2000 to 27.92 (27.06, 28.81) in 2015. Age-standardisation resulted in little change to these estimates. Whilst differences in incidence rates were seen by attained age, time since index osteoarthritis consultation, gender, and geographical region, the increasing trend over time was seen in all strata. The proportions of first gabapentinoid prescriptions in this cohort that could be attributed to osteoarthritis, a licensed indication, or an unlicensed indication were estimated as 9-10%, 11-12%, and 1-2%, respectively. This proportion of attribution remained relatively stable throughout the study period.

Patients with OA have become increasingly likely to be prescribed a gabapentinoid in the past two decades. Whilst this analysis found that the proportion of first prescriptions attributed to OA is approximately 9-10%, an unknown proportion of unattributed prescriptions may also be for OA. With growing concerns regarding their use, gabapentinoid prescribing in this condition requires careful justification.

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Abbreviations

ACR	American College of Rheumatology
ARUK	Arthritis Research UK
BMI	Body Mass Index
BNF	British National Formulary
CI	Confidence Interval (95% unless otherwise stated)
CPRD	Clinical Practice Research Datalink
CRPS	Complex Regional Pain Syndrome
EMA	European Medicines Agency
EU	Europe
FDA	Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GAD	Generalised Anxiety Disorder
GBD	Global Burden of Disease
GP	General Practitioner
GPRD	General Practice Research Datalink
HES	Hospital Episode Statistics
IASP	International Association for the Study of Pain
IMD	Index of Multiple Deprivation
IQR	Interquartile Range
ISAC	Independent Scientific Advisory Committee
MIA	Monoiodoacetate
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NJR	National Joint Registry
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
ONS	Office for National Statistics
PRN	Pro re Nata (in the context of medication: as required)
QST	Quantitative Sensory Testing
RA	Rheumatoid Arthritis
TCA	Tricyclic Antidepressants
THIN	The Health Improvement Network
TKA	Total Knee Arthroplasty
UK	United Kingdom
US	United States
WHO	World Health Organisation
WOMAC	The Western Ontario and McMaster Universities Osteoarthritis Index
YLD	Years Lived with Disability

1 The Epidemiology and Management of Osteoarthritis

1.1 Introduction

Osteoarthritis (OA) is the most common form of arthritis, and as one of the most prevalent chronic diseases worldwide, is associated with substantial healthcare demand. This thesis investigates the off-label use of a class of drugs, the gabapentinoids, in patients with osteoarthritis presenting to primary care in the United Kingdom. Specifically this work aims to understand the risk of a patient with OA receiving a gabapentinoid. To set this work in context, this chapter aims to provide a brief overview of the epidemiology and current management of the condition.

1.2 Defining Osteoarthritis

In epidemiology, it is imperative to identify the definition of the disease to be studied (Bhopal, 2008). Disease definitions influence estimates of the frequency of the disease in populations and the nature of cases recruited into observational studies and clinical trials. Current opinion is that OA is a complex set of disorders (Driban et al., 2010) and, similar to other chronic non-communicable diseases, several definitions are used within epidemiological studies. The multiple definitions of OA reflect the lack of a 'gold-standard' diagnostic investigation, differences in the nature, risk factors and prognosis of the disease across different joint sites and the various sources of available data for epidemiological research. Another contributor to the variety of OA definitions used may be the different perspectives on how OA is most usefully characterised, for instance as a clinical syndrome

of joint pain and associated symptoms (Thomas et al., 2004), or as a biomechanically-driven disease affecting synovial joints (Brandt et al., 2008).

Methods to define OA include using published classification criteria, such as those of the American College of Rheumatology (ACR), and other clinical guidance such as that provided by the United Kingdom's National Institute for Health and Care Excellence (NICE). NICE's guidance recommends the use of clinical criteria for diagnosing OA, based upon the presence of symptoms, such as stiffness and pain, in patients aged older than 45 years (National Institute for Health and Care Excellence [NICE], 2014). The ACR classification criteria for the diagnosis of knee, hip and hand OA are similar. Together with evidence of symptomatic disease, their diagnostic criteria also include signs elicited from physical examination, such as joint crepitus, as well as x-ray and laboratory findings (Altman et al., 1986, 1990, 1991). Large population studies have used doctor-diagnosed OA, or the self-reporting by study participants of persistent pain in joints commonly affected by OA, as indicative of the condition (Steel et al., 2014; Thomas et al., 2014). Some studies have relied upon evidence of disease found at post-mortem (Wallace et al., 2017). Electronic patient records and administrative healthcare records have increasingly been used to identify diagnoses for numerous conditions (Casey et al., 2016), and have been used in the study of osteoarthritis in the UK and internationally (Jackson et al., 2017; Jordan et al., 2007, 2014; Yu et al., 2015). Joint arthroplasty, a common endpoint for patients with severe OA, has also been used as a case definition, for example in genome-wide association studies (GWAS) (Zeggini et al., 2012).

Joint imaging is commonly used to define OA in epidemiological research. The Kellgren-Lawrence system, which utilises plain x-rays, is the most common method for defining OA radiographically (Braun & Gold, 2012). This system, approved by the World Health

Organisation (WHO), ranges from grade 0, with no radiographic evidence of joint pathology present, to grade 4, a joint with evidence of significant structural disease. Kellgren-Lawrence grade 2, defined by the presence of a definite osteophyte (Figure 1.1), is most commonly used by studies as their threshold to define OA (Lawrence, 1977; Schiphof et al., 2008). However, the use of the Kellgren-Lawrence system in epidemiological research has recognised limitations. Firstly, the use of grade 2 may result in conservative estimates of the prevalence of OA compared to clinical diagnoses, as patients who are judged to be grade 1 will be excluded, irrespective of their pain status. In the United Kingdom (UK) these patients could have a doctor-diagnosis of OA, as this can be made clinically without the need for radiographic investigations (NICE, 2014).[1] Secondly, the definitions, particularly of grade 2, have been used inconsistently in the literature, including by the original authors (Schiphof et al., 2008). In other studies, whilst many use the presence of an osteophyte in their grade 2 definition, the presence of joint space narrowing features inconsistently (Arden & Nevitt, 2006; Cross et al., 2014; Culvenor et al., 2015; Parsons et al., 2015). The dependence on osteophyte formation has also been reported to be a limitation, as patients with joint space narrowing who have no osteophyte development rarely fulfil the criteria to be defined as having OA (Kohn et al., 2016). The reliance on osteophyte formation has also been reported to be of limited use for the assessment of the disease progression of OA, leading to other intermediate grades being proposed (Felson et al., 2011). In summary, not only could studies be significantly under-reporting the prevalence of OA, but estimates of the prevalence of radiographic OA may be heterogeneous due to the inconsistent definitions used by epidemiological studies.

[1] The term 'doctor-diagnosis' describes a diagnosis provided by any healthcare professional.

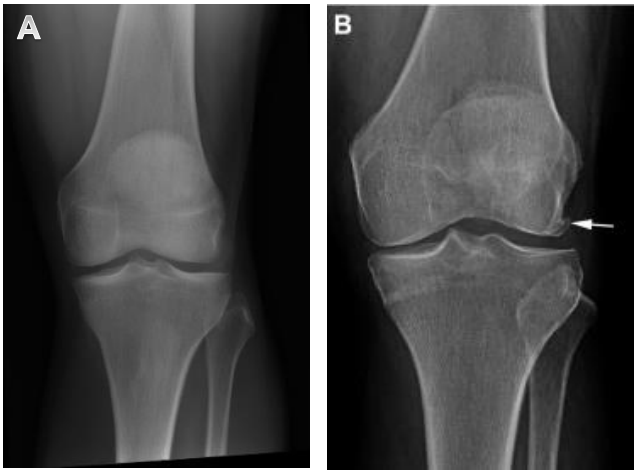


Figure 1.1 Knee X-rays to Demonstrate a Kellgren-Lawrence Grade 2 Knee

Image A depicts a normal knee (Radiopaedia, 2017), while B depicts a Grade 2 Kellgren-Lawrence knee, with a definite osteophyte, indicated by the arrow (Hayashi et al., 2016).

A limitation of the use of plain radiography is that the articular cartilage, one of the main tissues affected early in OA, is poorly visualised. Potentially in response to this, studies have explored the use of magnetic resonance imaging (MRI). A 2014 study found that a grading system for OA using MRI had better content validity and was more sensitive than the Kellgren-Lawrence system, and this increased sensitivity had a higher association with knee pain (Schiphof et al., 2014). However, currently MRI scans are costly, time-intensive and can cause anxiety in some patients, and as a result have seldom featured as the method of defining OA in large-scale epidemiological studies.

Whilst each of the definitions mentioned has strengths and limitations, they cannot be assumed to be directly comparable. A systematic review found the proportion of those with knee pain, who also had radiographically defined OA, ranged from 15 to 76% (Bedson & Croft, 2008). More recently, a systematic review reported that in asymptomatic adults aged ≥40 years, the prevalence of knee OA based on MRI ranged from 19-43% (Culvenor et al., 2018). As a result there may be vast differences between studies that use purely symptomatic or radiographic evidence versus those that use a combination of both definitions. It has also been demonstrated that a radiographic definition of OA leads to the

highest prevalence estimates, whilst self-reported and symptomatic definitions of OA produce similar results (Pereira et al., 2011).

To account for the inconsistencies in the definition used to estimate the prevalence of OA, the 2010 Global Burden of Disease (GBD) study used statistical modelling techniques to adjust for prevalence figures reported by studies that used definitions different from their reference standard. In this study their reference definition was symptomatic OA confirmed using radiography (Kellgren-Lawrence grade 2), perhaps the most commonly used definition (Cross et al., 2014).

1.3 Measures of the Frequency of Osteoarthritis

1.3.1 Prevalence

Using data from the Global Health Data Exchange, hosted by the Institute for Health Metrics and Evaluation, the worldwide age-standardised prevalence of symptomatic radiographic OA in 2016 was estimated as 4.5% (Institute for Health Metrics and Evaluation, 2017). As demonstrated by Figure 1.2, the estimated prevalence of OA is highest in high-income countries, such as the UK. The prevalence is also higher in females than males across all age groups and geographical locations, except in 30-39 year olds in high-income countries. The prevalence of symptomatic radiographic OA is strongly age-related, with prevalence negligible in children and adolescents and increasing in frequency across adulthood to exceed 5% after 45 years of age. As a result, many studies provide prevalence estimates within older age groups rather than in the whole population. For instance, an analysis of a Swedish healthcare register found that 26.6% of patients aged ≥45 years,

residing in the Skåne region in 2012 (n = 531,254), had received a doctor-diagnosis of OA affecting any joint (excluding the spine) at least once within the preceding 14 years. 13.8% of the population aged over 45 years had a diagnosis of knee OA, making it the most commonly affected joint (Turkiewicz et al., 2014). Although OA often affects the spine and hands, amongst other joints, the knee and the hip are the most frequently studied. Indeed, these two joints were the only sites analysed by the 2010 GBD study, which found the global age-standardised prevalence of knee and hip OA to be 3.8% and 0.85%, respectively (Cross et al., 2014). The focus on hip and knee OA may be justified by their frequency, debilitating nature, and relevance to joint replacements (National Joint Registry, 2017). However, it is likely that prevalence estimates based on these two joints alone will under-estimate the prevalence of OA due to the lack of accounting for spinal OA and other peripheral joint OA, which are often categorised as 'other musculoskeletal disorders'.

One of the first studies to assess the prevalence of knee OA was conducted by Felson et al. (1987), using the Framingham Heart Study cohort. The age-standardised prevalence of radiographic knee OA within this cohort was found to be 19.2% in patients aged ≥45 years, although, as pointed out by the authors, this may be limited by a lack of ethnic diversity within the population studied. Since a 2001 review compared the prevalence of knee pain with and without disability and radiographic changes (Peat et al., 2001), published prevalence studies specific to the UK are sparse. However, albeit slightly out of date, data can be obtained from Arthritis Research UK (ARUK). ARUK's Musculoskeletal Calculator, which utilises data from the Office for National Statistics (ONS), provides an estimate of 10.9% and 18.2%, respectively, for hip and knee OA in England in 2012, in patients aged ≥45 years (Arthritis Research UK, 2012). This translates to 2.5 million and 4.1 million sufferers of hip and knee OA in England in 2012, respectively (Public Health England, 2017).

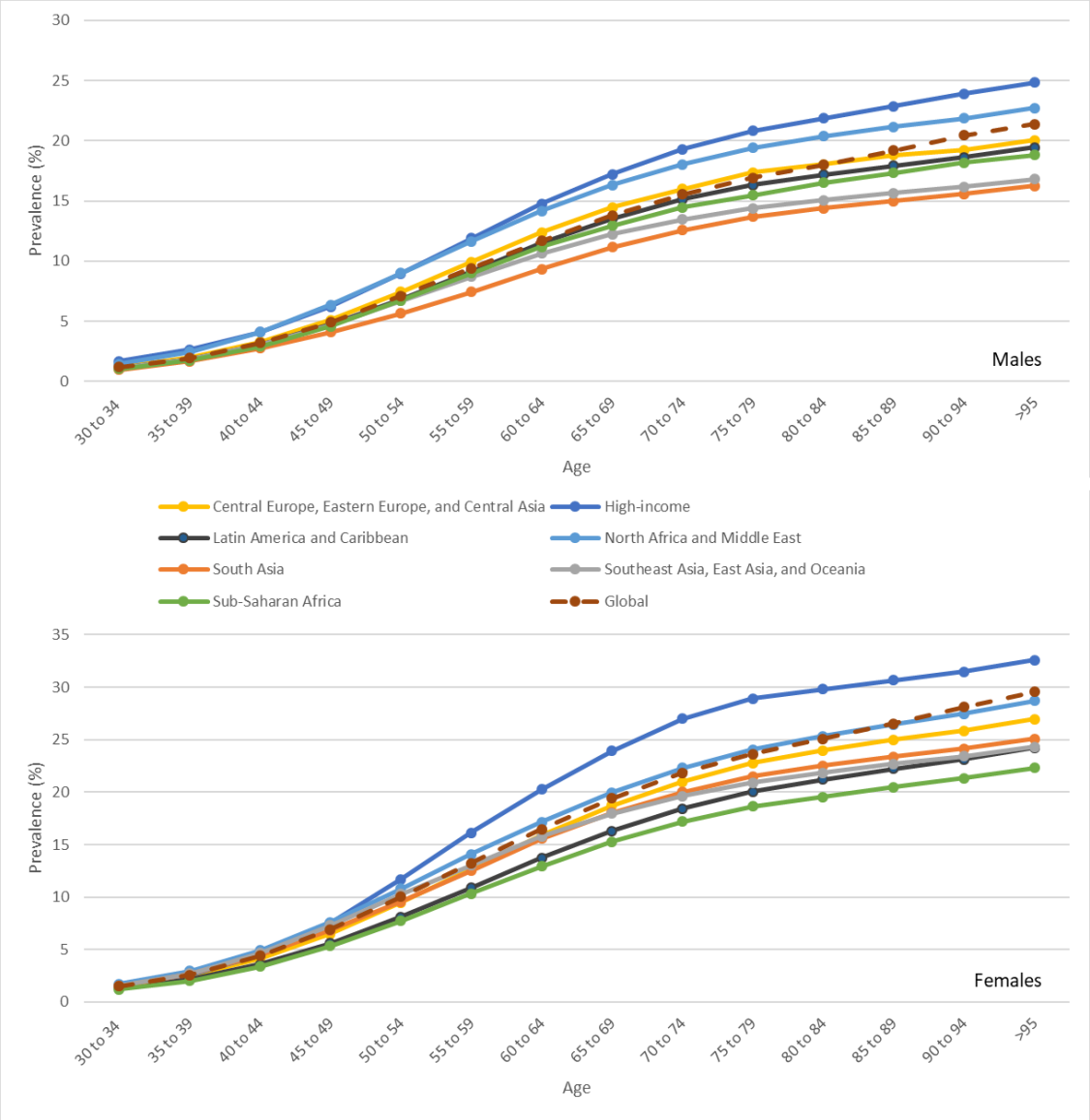


Figure 1.2 2016 Worldwide OA Prevalence, of Males (Top) and Females (Bottom), by Age and Location (Institute for Health Metrics and Evaluation, 2017)

The general consensus is that the prevalence of OA is increasing. Although this was not found in the 2010 GBD study, the authors noted that this finding was potentially due to the modelling software used to predict the prevalence of OA in countries where data were sparse, or due to the length of the study period (Cross et al., 2014). A recent analysis of more than 2,500 cadavers demonstrated that the prevalence of knee OA in those aged ≥50 years in the United States (US) has more than doubled between the early industrial (up to early 1900s) and post-industrial (late 1900s onwards) periods (Wallace et al., 2017). Between 2005 and 2015, the global prevalence count of knee OA for all ages increased

32.9%, although this increase reduced to 2.2% after the population was age-standardised (Vos et al., 2016). This may demonstrate the effect of the ageing population on the prevalence of OA. With both life expectancy and the proportion of the population who are elderly expected to increase, this growth is only expected to continue.

An increase in key determinants of OA may also contribute to its rising prevalence. Obesity is an important risk factor for the development and progression of OA, particularly of the knee (Allen & Golightly, 2015; Arden & Nevitt, 2006), and if projections are correct, the rise in prevalence of obesity will further compound the increasing prevalence of OA (Wang et al., 2011). After accounting for the projected changes in sex, age and obesity, Turkiewicz et al. (2014) predict that in Skåne, the region in Sweden, the prevalence of OA in patients aged ≥45 years will increase from 26.6% in 2012 to 29.5% by 2032, and over half of this total figure will remain accounted for by OA of the knee (13.8% in 2012, 15.7% in 2032).

1.3.2 Incidence

Estimates of incidence, the number of new cases within a population during a certain period of time, are much less commonly published than those of prevalence for a condition such as OA. One factor that may contribute to this is that identifying the precise time of onset may be difficult, and there may be a 'pre-clinical' phase before changes in radiography and symptoms manifest (Ryd et al., 2015). Alongside this delay between disease onset and the development of symptoms or radiographic changes, there may also be a delay between the development of symptoms and patients receiving a diagnosis of OA. A case-control study within North Staffordshire (UK) found that the median time between a patient's first knee symptom and their first diagnosis of knee OA in electronic healthcare records was 10.0 years (Bedson et al., 2005). OA was not assessed as part of the

incidence analysis of the 2015 GBD study, as they focussed instead on acute conditions such as infectious diseases (Vos et al., 2016). However, the reporting of incidence can be useful for chronic conditions such as OA as, without the influence of disease duration, it allows the temporal sequence of exposure and outcome to be studied. This allows the potential identification of risk factors, and the possible modification of these factors is extremely important from a public health perspective.

A study within British Columbia, Canada, reported that within the fiscal year 2008/2009 the crude incidence rate of OA in the total population was 14.6 cases per 1,000 person-years. Whilst the crude incidence rate had increased from 1991/1992, the age-standardised incidence only increased slightly in males and no change was observed in the incidence of OA in females (Rahman et al., 2014). As with prevalence, the definition used has a large effect on the incidence rates of OA reported by studies. For instance within the UK, a study of primary care data between 1992 and 2013 found that the age-sex standardised incidence rate of OA in any joint, recorded using clinical terms such as joint pain, in those aged ≥45 years, increased from 29.2 to 40.5 cases per 1,000 person-years. However, this increase was contrasted by incidence rates of consultations recorded as definitive, diagnostic OA, where the incidence rate fell from 8.1 to 6.3 cases per 1,000 person-years during the same period (Yu et al., 2017). This discrepancy in rates demonstrates the effect of different codes used in electronic healthcare databases, however NICE's clinical definition may also be a factor, leading to more diagnoses, irrespective of the incidence rate of OA diagnosed using prior criteria. Within Europe, a Spanish five-year cohort study of electronic healthcare records conducted between 2006 and 2010 reported the incidence rate of OA, stratified by joint. The incidence rate of hand, hip and knee OA was 2.4, 2.1 and 6.5 per 1,000 person-

years, respectively. This demonstrates again that, much like prevalence, knee OA is the most commonly affected joint (Prieto-Alhambra et al., 2014).

1.4 Risk Factors

Risk factors for OA can be general to all joints or joint-specific. Increasing age has been associated with the development of OA in all commonly affected joints (van Saase et al., 1989). However, the two may be independent processes, with ageing associated with factors such as impaired sensory innervation function (Arendt-Nielsen, 2017) as well as inflammation and oxidative stress, which in turn may contribute to the susceptibility of the joint to the development of OA (Loeser et al., 2016). There is also evidence that increasing age may be associated with OA due to the longer time frame for cumulative exposures, such as knee loading, to have an effect. This accumulation of excessive or repetitive mechanical loading may be influenced by occupation and activity (Andersen et al., 2012; Ratzlaff et al., 2012; Verbeek et al., 2017), and by an increased body mass (Wills et al., 2012).

There is evidence that certain risk factors have stronger associations with certain joints. For example knee OA is strongly associated with an increased body mass index (BMI), but this relationship is not seen in hip OA (Dieppe & Kirwan, 1994). This may explain why the BMI of patients tends to be higher in those undergoing knee arthroplasty, compared to those awaiting hip arthroplasty (Culliford et al., 2015). Evidence of the role of certain risk factors remains poorly understood, and in some cases, contradictory. For instance Visser et al. (2015) found that an increase in weight was associated with knee OA, after adjustment for metabolic factors, but no relationship between knee OA and metabolic factors was found

after adjusting for weight. Whilst the opposite was seen when studying hand OA, interestingly the relationship seen in knee OA was also found when studying patients with both knee and hand OA, suggesting there may be a more complex underlying relationship present. However, others have found an association between metabolic syndrome and knee OA (Wang et al., 2016), and a cumulative effect of increasing metabolic conditions and their association with knee, but not hip, OA (Monira Hussain et al., 2014).

One of the most recent systematic reviews of OA risk factors reported that knee OA was associated with having previous joint trauma, an increased BMI, and being female (Table 1.1). Previously studied risk factors, including smoking and concomitant hand OA, were not found to be associated (Silverwood et al., 2015). The effect of occupation on OA has also been studied. Manual labour is associated with knee OA, especially in males, whilst agriculture and farming has a strong association with hip OA (Andersen et al., 2012).

Table 1.1 Pooled Odds Ratios of Knee OA Risk Factors with 95% Confidence Intervals (CI) (Silverwood et al., 2015)

Risk Factor	Number of Studies	Total number of participants	Pooled Odds Ratio	Lower CI	Upper CI
Overweight	22	398,251	1.98	1.57	2.20
Obese	22	401,119	2.66	2.15	3.28
Overweight or Obese	25	415,613	2.10	1.82	2.42
Previous knee injury	13	27,326	2.83	1.91	4.19
Female Gender	11	28,133	1.68	1.37	2.07
Hand OA	6	5,232	1.30	0.90	1.87
Smoking	13	362,061	0.92	0.83	1.01

Evidence on the genetic contribution to OA is also expanding. Analysis has evolved from loci mapping (Zeggini et al., 2012) to functional analysis (Loughlin, 2015), although larger studies are required, especially as heterogeneity has been found between the studied joint sites.

1.5 Impact

As OA is a prevalent chronic painful condition, the impact it has on patients, healthcare services and wider society is large. In 2010, OA represented 2.2% of all years lived with disability (YLD), of which 83% were due to knee OA. Hip and knee OA combined ranked 11th out of the 291 conditions studied. This was an increase from rank 15th in 1990, demonstrating that the impact of OA is growing at a rate above that of other conditions (Cross et al., 2014).

On a personal level, OA can have a variety of effects on the patient. The most debilitating symptom is pain, and this is one of the 'need factors' that results in patients seeking medical advice (Paskins et al., 2013). The large impact OA may have on a patient's mobility may have large consequences in terms of work, but also on their general activities of daily living. Potentially because of this, as well as the physical impact, OA can also have psychological and emotional effects (Litwic et al., 2013). This emotional aspect to OA is important, as not only are anxiety and depression common in patients with OA, but both can negatively contribute to the experience of pain (Neogi, 2013). The wide range of effects of the condition results in patients with knee OA reporting lower health-related quality of life scores compared to age-matched controls and this relationship strengthens as the disease progresses (Farr II et al., 2013).

Prevalent diseases, especially those with high levels of disability, would be expected to impact heavily on healthcare providers. More than one third of patients aged 45 years or older consulted for OA during a seven-year prevalence study in North Staffordshire, England (Jordan et al., 2014). A Swedish study assessed the proportion of patients with OA who present to a doctor due to their osteoarthritis. Using a cohort of patients with symptomatic knee OA, they found that more than 74% consulted a doctor and received a

consultation code of knee OA or joint pain between 2004 and 2011. 63% of the same population consulted during this time period and received a consultation of knee OA specifically, after search terms were restricted (Turkiewicz et al., 2015). With many patients seeking medical attention for such a prevalent disease, this results in a large burden on health providers, both within primary and secondary care. As could be expected due to its increased prevalence compared to any other joint, knee OA results in the most recorded consultations in primary care (Yu et al., 2015). For secondary care, the number of admissions to consultant care is published by ARUK, using data from Hospital Episode Statistics (HES). In 2016/2017, they reported that musculoskeletal conditions accounted for 1.4 million admissions to consultant care, resulting in more than 2.2 million bed days (Arthritis Research UK, 2018). Whilst ARUK's information is not broken down by specific disease, such as OA, the National Joint Registry (NJR) may be a useful resource. This is a database of all joint replacements performed in England, Wales, Northern Ireland and the Isle of Man. Their published annual reports present the number of joint replacements, as well as other information, such as indications for surgery. In 2016, 98,147 primary knee and 87,733 primary hip arthroplasties were performed, of which greater than 96% and 90% were for the management of OA, respectively (National Joint Registry, 2017). This not only gives an idea of OA's impact on secondary care, but may give an indication of the prevalence of more severe OA within these nations. However, its use for this may be limited as it does not account for those patients that do not require, decline, or who are not deemed suitable for surgery. Secondly, although data is published on 'primary knee arthroplasties', which excludes surgical revisions, it is possible patients are included twice if they have had arthroplasties on both knees.

The debilitating nature of the condition also results in a large impact on the economy, estimated by a systematic review to be between 0.25 and 0.5% of a country's gross domestic product (Puig-Junoy & Ruiz Zamora, 2015). This burden can be divided into direct and indirect costs. Direct costs, such as the pharmacological treatment and surgery, have been estimated to account for 86% of the total economic burden of OA (Chen et al., 2012). A large proportion of the direct costs are due to the expensive surgical procedures and their associated expenditure, as a recent American study found that the marked rise of knee replacements now costs their economy $10.2 billion (£8.3 billion) annually (Ferket et al., 2017). Indirect costs incorporate days lost off work, and the associated loss of productivity and potential disability payments. Although data directly related to OA are sparse, musculoskeletal disorders resulted in 30.8 million days lost off work in 2016, representing 22.4% of the total (Office for National Statistics, 2017d). It should be noted that if, for instance, pharmacological therapies are cost-effective and allow a patient to return to work, direct costs may reduce indirect costs. However for a condition such as OA, current treatments are not always effective and the experience of adverse effects can result in further expenditure. The cost to the Canadian economy of these effects was estimated to be $316 million (~£200 million) in 2010, and is predicted to rise to $665 million by 2031 (Sharif et al., 2015). In the UK, a 1999 study assessed the cost of gastro-intestinal adverse effects experienced by patients prescribed non-steroidal anti-inflammatory drugs (NSAIDs). They estimated that the annual cost of adverse effects in this group of patients was £251 million, or £48 per individual (Moore & Phillips, 1999). More up to date information related to the UK is lacking, of both studies assessing the cost of the adverse effects of pharmacological OA management, or of the medications individually.

Whilst there has been increasing interest in the study of the economic costs of OA over the last decade, several issues remain. For instance, Chen et al. (2012) highlighted that current estimates may be conservative, due to factors such as there being no recognised way to identify indirect costs effectively, as well as a lack of accounting for alternative therapies in direct cost estimates, which are commonly used and result in large expenditure. There are also large differences between studies in their estimates of direct and indirect costs, potentially due to inconsistent methodologies. This not only makes the evaluation of the global impact of OA challenging, but means attempts to apply other country's data to the UK, where information remains sparse, are difficult. The review article by Chen et al. (2012) found no published studies regarding the direct and indirect costs of OA to the UK economy, and there has been little development. One of the most recent systematic reviews included 32 studies, of which none were from the UK (Salmon et al., 2016). As a result, obtaining data again relies on sources such as ARUK. Using information from an unpublished report, they estimate that the total combined direct costs of OA and rheumatoid arthritis (RA) will be £10.2 billion in 2018 alone (Arthritis Research UK, 2018). As could be expected due to the predicted increase in prevalence of OA, the costs associated with this condition are also projected to increase. This will largely be driven by increasing direct costs, and over the next decade, ARUK predict that the cumulative healthcare costs of OA and RA will be £118.6 billion (Arthritis Research UK, 2018).

1.6 Current Management

Within the UK, guidelines for clinical practice and patient management are published by NICE. The current guidelines for the management of osteoarthritis were released in 2014 (NICE, 2014). They recommend the treatment of OA be a holistic approach, with non-pharmacological, pharmacological and surgical options offered by the healthcare provider, alongside self-management by the patient (Figure 1.3).

The core elements of patient self-management are exercise and weight loss, if appropriate, as well as being provided with appropriate information. For lower limb arthritis advice regarding the use of appropriate footwear is also recommended. Non-pharmacological options are offered as adjuncts to the core treatments, and examples include thermotherapy, electrotherapy and the use of assistive devices.

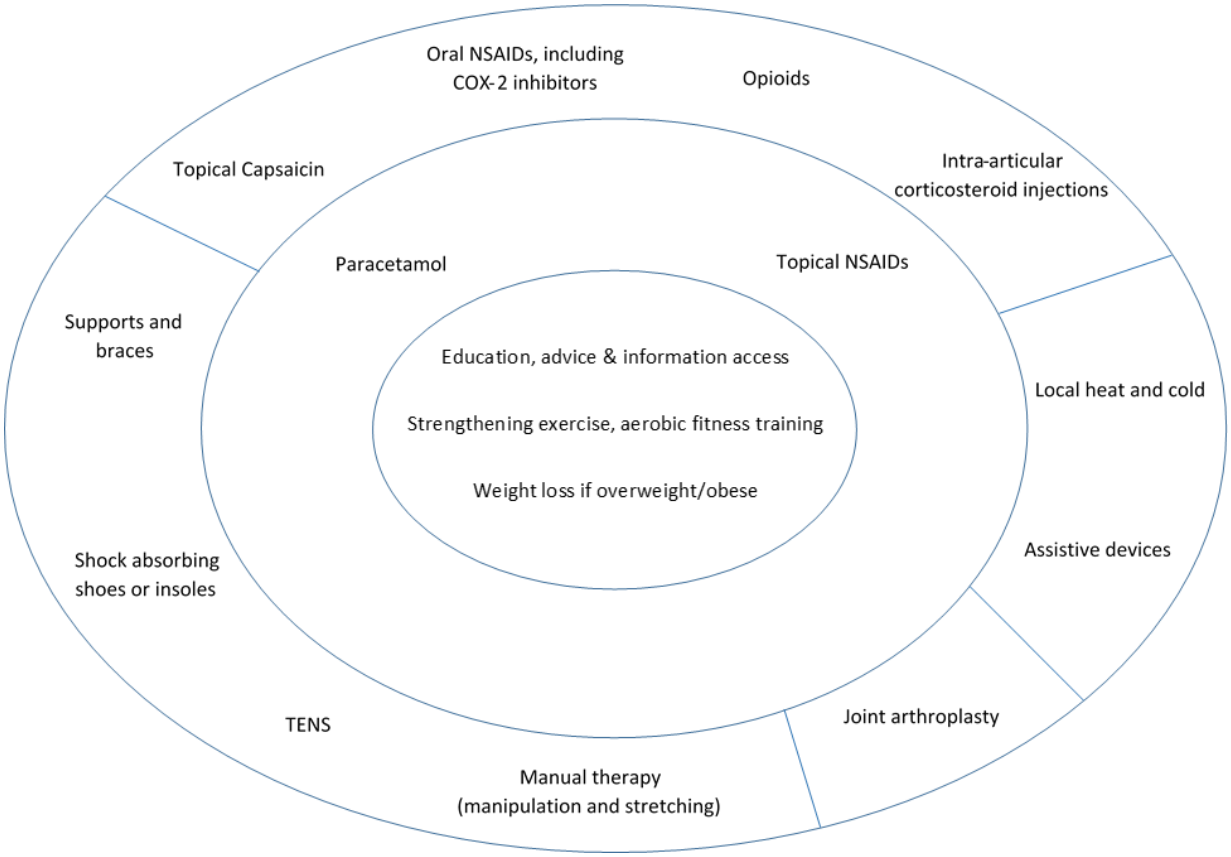


Figure 1.3 Management of Osteoarthritis, as Recommended by NICE (NICE, 2014)

Current pharmacological guidelines for OA advise the use of paracetamol or topical non-steroidal anti-inflammatory drugs (NSAIDs) as first line analgesic options. If required, they can also be used in combination. If this proves insufficient the introduction of an oral NSAID, COX-2 inhibitor or opioid is advised, if not contraindicated. Other options recommended for OA include intra-articular steroids, and for hand and knee OA, topical capsaicin (NICE, 2014).

Total joint arthroplasty is the definitive surgical treatment for OA. Arthroplasty is both clinically and cost effective, especially for knee and hip arthroplasty, the two most commonly replaced joints (Daigle et al., 2012; National Joint Registry, 2017; Pinedo-Villanueva et al., 2014). Arthroscopy with lavage was previously indicated for use in knee OA, but its routine use was found to have limited benefits that did not outweigh the risks, such as surgical complications (Reichenbach et al., 2010; Siemieniuk et al., 2017; Thorlund et al., 2015). As a result NICE do not recommend its use unless the patient has a specific clinical history, such as the knee locking or giving way (NICE, 2014).

1.7 Problems with the Current Management Options for Osteoarthritis

Problems with the current management approach of OA have been highlighted by recent literature. These include questions regarding the efficacy of pharmacological options, worries about their safety profiles, and the frequency at which they are contraindicated due to comorbidities (Machado et al., 2015; Roberts et al., 2016; Van de Laar et al., 2012; Vergne-salle, 2015). This may result in patients receiving suboptimal pain control, or being exposed to adverse effects.

Although patient self-management is central to the recommended management of OA, there is clear scope for improvements in supported behaviour change. Whilst studies have suggested that the role of exercise should be further encouraged for patients with conditions such as back pain and OA (Mallen & Hay, 2016), there is evidence that patients do not perform the recommended levels of exercise, and that clinicians also under-utilise provided services, such as physiotherapy. A study of data from the European Project on Osteoarthritis (EPOSA) reported that patients with knee OA, compared to those without, are more inactive and less likely to follow physical activity recommendations (Herbolsheimer et al., 2016). A study of general practices in the West Midlands of the UK reported that only 36% of applicable OA consultations resulted in a consideration of a referral to physiotherapy, compared to the 63% which were considered for pain assessment (Edwards et al., 2014). Similarly, a Danish study of general practices in the UK, Denmark, Portugal and Norway reported that only 11% of applicable OA consultations resulted in a referral to services to assist in losing weight (Østeras et al., 2015). It is therefore clear that this core treatment approach is not fully optimised. Potentially in response to this under-utilisation and lack of effective communication between healthcare professionals and patients, studies have explored the effect of using the internet or telephone consultations to increase the information that patients receive (Lane et al., 2017).

Within the pharmacological guidelines for managing OA, there is no explicit mention that the approach taken by doctors should be step-wise. However, the concept of the guidelines, whereby if one step proves insufficient it is replaced by a stronger analgesic, could be viewed as such. Some have deemed the use of this approach to analgesia inadequate for chronic pain. Compared to acute and end of life pain, chronic pain tends to

have a very unpredictable trajectory, affected by factors such as mood and circumstance (Ballantyne et al., 2016). As a result a ladder, where the majority of patients often only move up to a more potent analgesic, does not take into account the variations in pain experienced. It has therefore been proposed that a stratified, rather than stepwise, approach may better accommodate for these fluctuations in pain.

Alongside the management approach of OA, there are growing concerns with the individual pharmacological medications recommended for use in patients with OA. It should be noted that whilst all therapies mentioned are effective in some patients, their use does not come without risk. Although paracetamol is the most widely used and prescribed drug in the UK (Dear et al., 2015), there have been growing concerns with its use. Classically viewed as an effective analgesic for a variety of conditions, until recently very few studies had assessed its effectiveness for chronic pain. A 2016 systematic review found that it had "negligible efficacy with doubtful clinical relevance" for chronic pain (Ennis et al., 2016, p. 188). Another found that irrespective of dose, paracetamol did not exceed the effect size threshold for chronic pain of -0.37, and thus had no role as a single agent in the treatment of OA (da Costa et al., 2017). Secondly, there are growing safety concerns with paracetamol. Although it is often seen as safe, especially compared to NSAIDs which it is commonly compared against, a systematic review reported that four trials had demonstrated a dose-response relationship between paracetamol and cardiovascular adverse effects. Of two studies that reported mortality, both demonstrated an increased risk with paracetamol use compared to placebo, and one trial found there to be a dose-response relationship present (Roberts et al., 2016). As highlighted by the authors of this systematic review, a common limitation for studies such as these is channelling bias. This inequality arises as patients are often started on a certain medication due to their risk of

adverse effects with other treatments. As a result it is challenging to compare intervention and control group participants, making inferences difficult. An adverse effect commonly associated with paracetamol use is hepatic damage. Although this is often a result of overdose, recent studies have demonstrated that this can occur when paracetamol is used at therapeutic doses. A 2015 systematic review reported that patients taking paracetamol were nearly four times more likely than those taking placebo to have elevated liver function test results, although the clinical importance of this was unclear (Machado et al., 2015). Another potential issue with paracetamol is its presence in a wide variety of over the counter products, including combination medications. This may lead to patients not being aware of the cumulative dose of 'hidden paracetamol' that they are taking (Van de Laar et al., 2012), resulting in an increased risk of adverse effects, due to taking a higher dose than the recommended daily maximum of four grams. Amid researchers concluding that the recommendation of paracetamol in guidelines should be reconsidered (Machado et al., 2015), the concerns with paracetamol have not gone unnoticed. In the drafted guidelines for the management of OA, NICE recommended that paracetamol should not be routinely used due to the uncertainty of the clinical benefit and possible adverse effects (National Clinical Guideline Centre, 2013). However, due to worries that this would lead to an increase in prescribing of NSAIDs and opioids, this was revised for the published guidelines, and paracetamol continues to be recommended.

There are also concerns with the use of NSAIDs, another class of drugs commonly used in patients with OA. Although a meta-analysis demonstrated that many NSAIDs are effective compared to placebo (da Costa et al., 2017), concerns remain regarding their use in OA. These are primarily related to adverse effects and them regularly being contraindicated due to the wide variety of comorbidities experienced by patients with OA. Common

adverse effects associated with NSAID use include cardiovascular and gastrointestinal events, as well as abnormal renal function (Bhala et al., 2013; Moore, Pollack, et al., 2015). The high risk of gastric ulceration in patients with OA prescribed an NSAID results in NICE recommending co-therapy with a proton pump inhibitor (PPI) to act as a protective agent (NICE, 2014). The risk, or having a history of, one of these adverse effects, as well as the potential for drug interactions, often results in NSAIDs being used with caution or contraindicated. As the number of medications prescribed to the elderly population rises (Melzer et al., 2015), this may result in the use of NSAIDs in many patients with OA becoming increasingly problematic. Interactions with aspirin, antihypertensives, antidepressants and corticosteroids have been reported by studies (Moore, Pollack, et al., 2015). Potentially due to the risks of NSAID use, NICE recommend that they be used at the lowest dose and for the shortest possible time (NICE, 2014). With recommendations such as these for drugs used as commonly as NSAIDs, it would appear that the current guidelines and treatment approach may not be congruent with the natural history of the disease.

Potentially due to NSAIDs not representing a suitable long term therapy, there has been a decrease in their use for patients with OA, and instead, patients have increasingly been prescribed opioids such as tramadol (Yu et al., 2017). Whilst opioids remain recommended by NICE for the management of OA (NICE, 2014), there are serious concerns with their use. Due to the high incidence of withdrawals in trials, Osteoarthritis Research Society International (OARSI) deem opioids of “uncertain appropriateness” for specific subgroups of patients with OA (McAlindon et al., 2014, p. 376). Although the Cochrane review of opioid use in hip and knee OA reported that patients benefitted marginally from their use, this observation was of questionable clinical significance. They also found an increased risk of severe adverse effects and dependency (da Costa et al., 2014). A 2018 randomised

controlled trial of patients with back pain or OA of the knee or hip found that opioid analgesics did not significantly improve pain-related function over the course of 12 months. Of the secondary outcomes, only anxiety improved for the patients taking opioids. This lack of analgesic efficacy resulted in the authors concluding that there is little support for the initiation of opioids in these chronic pain conditions, as the advantages did not outweigh the risk of harms, as medication-related adverse effects were more common in the group of patients taking opioids (Krebs et al., 2018). There are also concerns with the misuse potential of opioids, with the increase in opioid related overdoses and deaths becoming widely known in the US as the 'opioid epidemic' (Manchikanti et al., 2012). Misuse is defined as the use of a medication either without one's own prescription or with a prescription but not using the medication as instructed. The 2015 National Survey on Drug Use and Health in the US reported that, of the 91.8 million (37.8%) US adults who were prescribed an opioid in 2015, more than 10% misused them. However, as almost 60% of patients who misused opioids did not receive them from a doctor, the authors highlighted the common diversion of opioids, with patients who misuse them often receiving them free from relatives or friends (Han et al., 2017).

Whilst arthroplasty is viewed by many as an effective, definitive treatment, issues do remain. Firstly, it does not result in adequate pain relief in all patients, with a large number reporting persistent pain post-operatively. After adjusting for losses to follow-up, a systematic review estimated the prevalence of post-operative pain following hip arthroplasty as between 7 and 23%, and between 10 and 34% for knee arthroplasty (Beswick et al., 2012). Secondly, the incidence of OA diagnoses in younger patients, such as in those aged 35-44 years, is increasing (Yu et al., 2015). As more than 10% of total knee arthroplasties require revision within 15 years (Niinimäki et al., 2014), the increasing

incidence of OA in younger patients, combined with increasing life expectancy, may become problematic unless changes are made to the prosthesis. These concerns, as well as the number of patients for whom surgery is not suitable, mean that analgesia will continue to be significantly important in the management of OA.

In conclusion, whilst more can be done to potentially optimise core treatments and surgical approaches, the main concerns are with the recommended pharmacological options for OA. Whilst some patients may gain some benefit from paracetamol, NSAIDs or opioids, this tends to be modest, and this must be balanced against the risk of harms, such as adverse effects. With studies demonstrating that patients are unwilling to risk adverse effects to potentially reduce pain (Hauber et al., 2013), there have been reports that clinicians are resorting to non-recommended therapies for conditions such as OA. There is also a growing number of studies exploring the possible pain mechanisms of OA, whilst others are studying the efficacy of other, non-guideline, therapeutic options for the pain of those with the condition.

1.8 The Pain Mechanisms Involved in Osteoarthritis Pain

Within the field of OA research, there has been a growing number of studies exploring the potential effectiveness of novel treatments, such as platelet rich plasma, as well as the use of therapies used for other conditions but not recommended for OA, such as bisphosphonates, calcitonin, and the supplements glucosamine and chondroitin (Lane et al., 2017). However, to date very few trials have demonstrated consistent effects on clinical outcomes of OA, and potentially due to trials not providing clear therapeutic solutions, there has been an expansion of the literature regarding the mechanisms of OA pain, which

some believe should be central to the focus of management guidelines (Van de Laar et al., 2012).

Historically, OA pain was viewed as purely nociceptive, arising from the damaged joint. Studies have demonstrated associations between pain and bone marrow lesions, synovitis and joint effusions (Fu et al., 2017; Thakur et al., 2014). However, the lack of response by some patients to conventional therapies, as well as the large discrepancy between the radiographic severity of OA and the intensity of pain experienced by the patient (French et al., 2017; Lee et al., 2011) has resulted in other mechanisms of pain being proposed. These include peripheral and central sensitisation, as well as neuropathic pain.

Whilst the affected joint is clearly the original source of pain in OA, there is evidence that abnormal pain processing by the nervous system may amplify or augment these signals, in a process known as sensitisation. Sensitisation can occur both centrally and peripherally, due to the neuroplasticity of the nervous system. The repetitive nociceptive stimuli arising from an osteoarthritic joint is thought to be the "main driver" of processes resulting in centralised sensitisation (Arendt-Nielsen, 2017, p. S-68). O'Driscoll and Jayson produced one of the earliest articles suggesting the presence of central sensitisation in OA. In their study they reported that patients with hip OA had a reduced pain threshold at the forehead, a site typically unaffected by OA (O'Driscoll & Jayson, 1974). More recently, Gwilym et al. (2009) utilised Quantitative Sensory Testing (QST) and neuroimaging in patients with and without OA. They found that patients with OA had lower thresholds to punctate stimuli, and MRI imaging demonstrated greater activation in the brainstem of patients with OA in response to noxious stimuli. Features of central sensitisation include allodynia (pain arising from typically non-painful stimuli), hyperalgesia (an increased sensitivity to pain) and alterations in the intensity and duration of pain. The use of pain

drawings has also demonstrated the altered extent to which patients with central sensitisation may experience pain (Fu et al., 2017; Lluch Girbes et al., 2016).

The development of peripheral sensitisation has been associated with inflammatory mediators in joints with OA, and tissues thought to be involved in this process include the articular cartilage and subchondral bone. Although the articular cartilage, one of the main tissues affected in OA, lacks innervation and vascularity in a normal joint (Dimitroulas et al., 2014), it has been proposed that the inflammatory process of OA may alter its structure. There is evidence to suggest that the cartilage of an osteoarthritic joint is infiltrated by neurons, and at arthroplasty, when compared to healthy joints, an increased presence of immune cells, growth factor expression and angiogenesis has been reported in osteoarthritic knees (Thakur et al., 2014). The cytokines and mediators responsible for the occurrence of angiogenesis in chronic inflammation may also cause sensitisation of local nerves, and this relationship between vascular growth and neural sensitisation has been proposed as a source of OA pain (Dimitroulas et al., 2014; Walsh, 2016). Support for the theory that sensitisation of peripheral nerves may also occur in the subchondral bone includes the fact that this densely innervated tissue is not affected until later in the disease, when OA pain is typically more severe (Ohtori et al., 2013).

Neuropathic pain has been proposed as a component in the pain experienced by some patients with OA. The International Association for the Study of Pain (IASP) define neuropathic pain as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (French et al., 2017; Jensen et al., 2011; Treede et al., 2009, p. 1361). By definition this lesion can occur both centrally and peripherally, and examples include spinal cord injuries and following joint surgery, respectively. A 2017 systematic review of 9 studies found that, within a population of patients with hip or knee OA, from

both the community and healthcare settings, the prevalence of neuropathic pain characteristics was 23% (95% CI: 10, 39). They did however express concerns with the variety of methodologies present, and believe certain studies may considerably overestimate the prevalence (French et al., 2017).

Whilst studies have attempted to detect neuropathic pain characteristics in patients with OA, the concept of neuropathic pain in OA needs to be viewed cautiously. IASP's definition of neuropathic pain was changed in 2008, removing the previously used word 'dysfunction', to distinguish 'true' neuropathic pain from pain arising from a dysfunctional somatosensory nervous system, for instance due to central sensitisation (Treede et al., 2009). Consequently, in order to be defined as neuropathic pain according to the latest definition, OA must be capable of causing a lesion of the somatosensory system. Whilst ATF-3, a protein marker of neuronal injury, has been detected in the dorsal root ganglions of rat models of OA induced by monoiodoacetate (Ivanavicius et al., 2007), a clear lesion to the somatosensory system has not been definitively identified. As a result, the symptoms reported by patients would be characteristics of, rather than indicative of, neuropathic pain – most likely resulting from central and peripheral sensitisation. This is often overlooked in studies, where conclusions are made that a certain proportion of patients with OA 'have neuropathic pain' (French et al., 2017). This would result in OA being viewed similarly to conditions such as fibromyalgia, where a definitive lesion is not always identified, or complex regional pain syndrome type 1, which by definition has no nerve lesion. The distinction created by the latest definition may be a reason for the separation of the previously combined Cochrane systematic reviews analysing the efficacy of the neuropathic pain medications gabapentin and pregabalin in neuropathic pain from their effectiveness in fibromyalgia. It should be noted that the latest Cochrane review studying

gabapentin in neuropathic pain made no mention of OA in the context of neuropathic pain. Indeed, they used an “arthritic knee” as an example of non-neuropathic pain (Wiffen et al., 2017, p. 2). As Cochrane reviews are often seen as the pinnacle within the literature hierarchy, and bearing in mind the prevalence of OA and the recent expansion of the field of research regarding neuropathic pain in OA, this omission is interesting.

Whilst there is no current gold standard for identifying patients with neuropathic pain (French et al., 2017), QST is often used, especially in research settings. However, this time-intensive approach is impractical clinically due to the large number of patients with OA, leaving a questionnaire as a more viable alternative. Questionnaires assessed by studies include the Douleur Neuropathique 4 (DN4) and the modified painDETECT (mPD-Q) (Aşkin et al., 2017). The mPD-Q, prior to modification for OA, was used to identify characteristics of neuropathic pain in patients with chronic low back pain (Hochman et al., 2011). It uses the presence of features such as allodynia and hyperalgesia to indicate the likelihood of the patient having neuropathic pain. Attempts have also been made to correlate risk factors with questionnaire scores, however no association has been found between high painDETECT scores and age or duration of disease (Mesci et al., 2016).

Whilst debate remains regarding the extent to which certain patients with OA have ‘true’, or merely characteristics of, neuropathic pain, the identification of these individuals may be beneficial for several reasons. Firstly, for patients with OA, the presence of neuropathic pain characteristics can negatively affect a patient’s function, quality of life and experience of pain (French et al., 2017; Valdes et al., 2014). Scores that have been used to assess the association been neuropathic pain characteristics and reduced quality of life include the Short Form-36 (SF-36) and the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) (Aşkin et al., 2017). The identification of these patients would then allow

more targeted medications to be prescribed for these pain mechanisms, where conventional OA management options such as NSAIDs and paracetamol are known to be of limited efficacy (Moore, Chi, et al., 2015). Examples of possibly effective analgesic therapies include some antidepressants and anticonvulsants, collectively known as neuromodulators. Identifying patients with neuropathic pain characteristics may also be important in the context of trials evaluating the efficacy of medications. Therapies such as the neuromodulators are rarely being studied with the view that they will be used for all patients with conditions such as OA and as a result it is critical to study their use in specific subgroups of patients. Without clearly identifying the study population, it is possible that the heterogeneity of patients within the study is nullifying the studied drugs' effectiveness, rather than the lack of observed efficacy being due to the ineffectiveness of the drug itself (Thakur et al., 2014). Further still, as recent neuropathic pain studies have attempted to stratify patients into different phenotypes to identify those best suited to certain therapies (Holbech et al., 2016), identifying those with a potential neuropathic element may be a minimum requirement.

In summary, there has been an expansion of the literature suggesting that the pain experienced by some patients with OA may have features of neuropathic pain. However, the lack of a clear somatosensory lesion means that OA may not fulfil the criteria to be defined as 'true' neuropathic pain, and as a result the features elicited by QST or questionnaires such as the painDETECT are most likely a consequence of central and peripheral sensitisation, which have similar characteristics. The presence of sensitisation may explain why certain groups of individuals do not respond to the analgesia currently recommended by NICE for the management of OA, and thus there may be a role for medications more tailored to these pain mechanisms, known as neuromodulators.

1.9 The Use of Neuromodulating Medications in Osteoarthritis

Neuromodulation is defined as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body" (The International Neuromodulation Society, 2018). There is a variety of chemical neuromodulating medicines that can be used, not just as analgesia, but to provide symptomatic relief in a variety of conditions, such as Parkinson's disease. Neuromodulating medicines currently recommended for neuropathic pain include the antidepressants duloxetine and amitriptyline and the anticonvulsants gabapentin and pregabalin (National Institute for Health and Care Excellence, 2013). Although there has been a growing body of evidence suggesting that the neuromodulators may be effective for some patients with OA, to date only the serotonin-noradrenaline reuptake inhibitor (SNRI) duloxetine is recommended by OARSI for knee OA (McAlindon et al., 2014), and no neuromodulators are currently recommended by NICE for the management of OA (NICE, 2014).

As one may expect clinicians to explore recommended options prior to prescribing a non-guideline medication, any use of such medications could be expected in patients with more severe OA. A potential marker of this is the period prior to arthroplasty. In a Norwegian study of patients prior to and following hip arthroplasty, Blågestad et al. (2016) reported that 8% of patients were prescribed an antidepressant three months prior to their arthroplasty. Other medications assessed were anxiolytics and hypnotics, which were collectively grouped with antidepressants as 'psychotropics', due to their effects on a patient's mental state. In total, 25.8% of patients were prescribed a psychotropic three months prior to their arthroplasty, and this increased in the three month period immediately post-operatively before returning to pre-operative levels. Although this study did not necessarily identify patients with OA, we know that this is the primary indication

for hip arthroplasty, and often comprises greater than 90% of the caseload (National Joint Registry, 2017).

Another class of medications with neuromodulating properties are the gabapentinoids gabapentin and pregabalin. In recent years within the UK, concerns have arisen regarding the substantial increase in gabapentinoid prescribing and their potential to be misused. Whilst it is thought that painful conditions are a large determinant of their increased prescribing, data regarding their use in OA are sparse. In a similar study to the one conducted by Blågestad et al. (2016), Inacio et al. (2018) assessed the proportion of patients who received a prescription for a gabapentinoid in the year prior to their joint arthroplasty. Gabapentin and pregabalin were analysed with the tricyclic anti-depressant (TCA) amitriptyline and collectively grouped as 'neuropathic pain medications'. They reported that the prevalence of patients (n = 15,517) prescribed a neuropathic pain medication in the one year prior to their knee arthroplasty increased from 5.2% in 2001 to 11.4% in 2012. A very similar trend during this time was also seen in patients before hip arthroplasty. This may point to a potential increase in the use of the gabapentinoids in patients with more severe OA. However, it is not understood whether OA is the reason for the prescribing of the gabapentinoids, and the prevalence of the use of such medications before and after arthroplasty, as assessed by Blågestad et al. (2016), may be accounted for by different patients.

1.10 Conclusion

OA is one of the most prevalent chronic health conditions worldwide, with most forecasts projecting further increases in the crude, if not age-standardised, prevalence of the condition in populations. A range of recommended management options currently exists, but few confer substantial benefits and there are particular problems with access to non-pharmacological treatments, the long-term safety of some pharmacological options, and the future affordability of the continued increases in demand for joint arthroplasty. These concerns have resulted in clinicians and researchers looking towards existing treatments not currently licensed (nor recommended) for OA. The rationale for the use of the neuromodulators in OA may have strengthened due to the proposed neuropathic component of the pain experienced by some patients with the condition. The high prevalence of OA means that such use has the potential to involve a large number of patients. Amid concerns regarding the substantial rise in prescribing and misuse potential of the gabapentinoids, the remainder of this thesis will focus on the use of gabapentin and pregabalin in OA. The next chapter will provide a brief overview of their history, followed by the possible rationale and efficacy of their use in this common, painful condition.

2 The Gabapentinoids

2.1 Introduction

The gabapentinoids gabapentin and pregabalin are analogues of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Whilst their precise mechanism of action is not completely understood, they do not exert their effects on the GABA receptor. Instead, they are thought to act on the α_2-δ-1 subunit of voltage gated calcium channels (Stahl et al., 2013). This results in them having several effects, acting as an anti-convulsant, anxiolytic and analgesic (Cappuzzo, 2009). Although other gabapentinoids are in trials or have been approved, such as mirogabalin and gabapentin enacarbil, respectively (Vinik et al., 2014), pregabalin and gabapentin are the only gabapentinoids currently prescribed in the UK and as a result these two medications will be the focus of this thesis.

2.2 History of the Licensing and Use of Gabapentin and Pregabalin

Gabapentin, branded as Neurontin, first entered the market in the United States (US) in 1993, manufactured by the Warner-Lambert subsidiary Parke-Davis. At this time it was initially licensed by the Food and Drug Administration (FDA) as an adjuvant in the therapy of the treatment of partial seizures in patients aged older than 12 years. Its use was extended to patients older than three years in 2000, before being licensed for post-herpetic neuralgia in 2002 (U.S. Food & Drug Administration, 2018). In Europe, the European Medicines Agency (EMA) first approved gabapentin in 2006, for use in epilepsy and peripheral neuropathic pain syndromes, such as painful diabetic neuropathy and post-

herpetic neuralgia (European Medicines Agency, 2006). In the UK, the latest British National Formulary (BNF) indicates that as of June 2018 gabapentin is indicated for epilepsy, peripheral neuropathic pain, migraine prophylaxis and for menopausal symptoms in women with breast cancer (Joint Formulary Committee, 2018).

Pregabalin, commonly branded as Lyrica, was produced after gabapentin, again manufactured by Parke-Davis. It was first licensed in July 2004 in Europe for use in epilepsy and as an analgesic in post-herpetic neuralgia and diabetic neuropathy. In 2006 its licence within Europe was extended to generalised anxiety disorder (Baldwin et al., 2015; European Medicines Agency, 2009a). The BNF lists pregabalin's indicated uses in the UK as generalised anxiety disorder, focal epilepsy and for both peripheral and central neuropathic pain (Joint Formulary Committee, 2018). Examples of central neuropathic pain include the pain experienced by patients following a stroke or spinal cord injury. Pregabalin was first approved in the US in December 2004 for peripheral neuropathic pain (Dworkin & Kirkpatrick, 2005), followed by an approval for fibromyalgia in 2007 (Cascade et al., 2008; Pfizer, 2016). Interestingly, an application for a license for pregabalin's use in fibromyalgia was refused by the European Medicines Agency in 2009. This was due to a lack of trial evidence in European populations, and concerns regarding pregabalin's clinical efficacy and safety (European Medicines Agency, 2009b).

A timeline of both gabapentinoids in Europe and the US is visually represented in Figure 2.1.

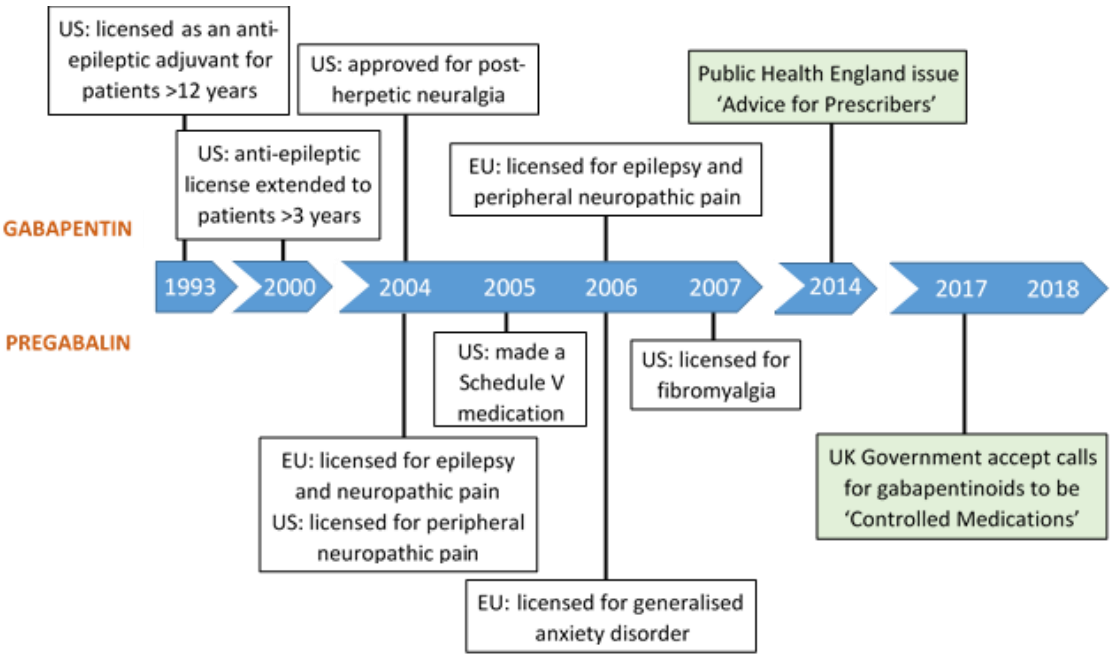


Figure 2.1 Timeline of Gabapentin (Top) and Pregabalin (Bottom) in the United States (US) and Europe (EU). Events Shaded Green Apply to Both Gabapentinoids

Data of all community issued prescriptions, from each of the four countries of the UK (England, Northern Ireland, Scotland and Wales), are published annually. Since 2004, the total number of gabapentinoids prescribed in the UK has risen sharply (Figure 2.2). In 2004, just over 1 million gabapentin prescriptions were issued. By 2010 this number had risen to almost 3 million prescriptions, and by 2016 was 7.8 million. Pregabalin has followed a similar trend. Since its approval in 2004, the number of items prescribed has risen from 24,640 to just over 6.7 million in 2016. To provide comparison, prescriptions of tramadol, an opioid analgesic included alongside the gabapentinoids in a recent report on dependence-forming medicines (Cartagena et al., 2017), have increased from 8.5 million in 2010 to 9.3 million in 2016 (Business Services Organisation, 2018; ISD Scotland, 2018; NHS Digital, 2017; Welsh Government, 2017). Using population data from the Office for National Statistics (Office for National Statistics, 2017c), the absolute number of gabapentinoid prescriptions can be presented as a rate per 1,000 individuals. When prescriptions of

gabapentin and pregabalin are combined, gabapentinoid prescribing has increased from almost 20 gabapentinoid prescriptions per 1,000 individuals (of any age) in 2004 to over 220 prescriptions per 1,000 individuals in 2016. The increase in gabapentinoid prescribing has also been observed in other countries. As of September 2017, gabapentin was the seventh most commonly prescribed medication in the US (GoodRx, 2017), with the total number of prescriptions rising 64% between 2012 and 2016. In the same period spending on pregabalin more than doubled (Goodman & Brett, 2017).

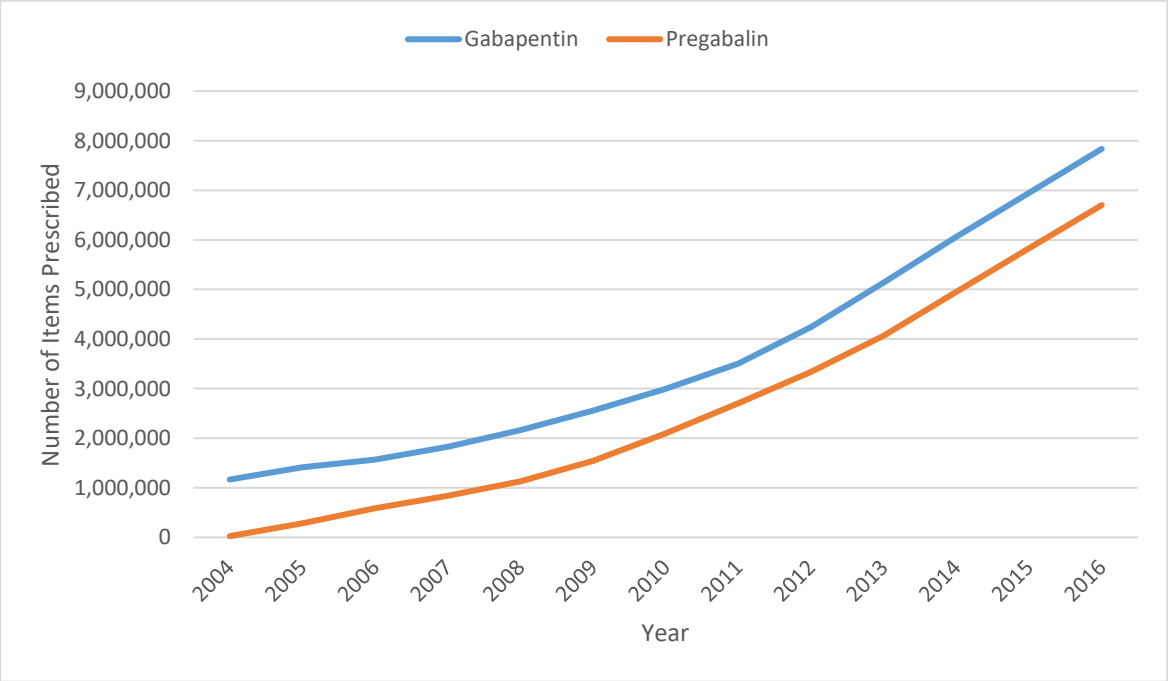


Figure 2.2 Annual Gabapentinoid Prescriptions in the UK, 2004-2016 (Business Services Organisation, 2018; ISD Scotland, 2018; NHS Digital, 2017; Welsh Government, 2017)

The observed increase in prescribing may be accounted for by several factors. Firstly, a change in the prevalence of the conditions for which the gabapentinoids are licensed may explain an increase in prescribing. For instance it is likely that the prevalence of painful diabetic neuropathy has increased, as the prevalence of diabetes in the UK increased from 3.2% to 5.3% between 2004 and 2014 (Zghebi et al., 2017). As the incidence of newly diagnosed diabetes decreased during this time, the observed rise in prevalence must be accounted for by greater disease duration. Secondly, the increasing number of licensed

indications of the gabapentinoids may also explain an increase in prescribing. For instance in Europe, pregabalin's license for generalised anxiety disorder (GAD) came two years after its approval as both an analgesic for neuropathic pain and anti-convulsant for epilepsy. As the lifetime prevalence of GAD has been estimated as almost 3% in Europe (Alonso et al., 2004), a license for this condition may have contributed to an increase in prescribing. Although there may be some delay between drug approval and its uptake in medical practice, it is felt that this change in licensing is unlikely to account for the dramatic rise in prescriptions witnessed since 2012, as most indication changes occurred before 2007. Changes in the population of patients prescribed a gabapentinoid may also influence prescribing, for instance if prescribing practices changed and the gabapentinoids were prescribed more commonly to older age groups. However, information regarding patient demographics is not readily available in national prescribing data. Even though all the above may contribute, expert consensus is that it is not felt that any of these factors can completely explain the substantial rise in prescriptions (Goodman & Brett, 2017). Instead, it has been postulated that the rising number of prescriptions for gabapentinoids reflect their increasing off-label use, i.e. for conditions for which they are not licensed.

There is evidence to suggest that the off-label use of the gabapentinoids could be substantial. A 2002 American review estimated that the off-label use of gabapentin was as high as 95% in a Medicaid population. Unlicensed conditions for which the drug were commonly used at this time included bipolar disorder and restless legs syndrome (Hamer et al., 2002). More recently, a study of patients with chronic non-cancer pain attending tertiary care centres in Canada found that 73% of pregabalin prescriptions were for unlicensed conditions, such as lumbar back pain with or without radiculopathy (Giladi et

al., 2015).[2] Whilst some variation exists between studies, potentially due to differences in methods and varying prescribing practices by geographical location, it is clear that both gabapentin and pregabalin have been prescribed for conditions beyond their respective licenses. A perspectives article assessing the reasoning for off-label prescribing by clinicians in Canada found that they rarely differentiated between licensed and non-licensed indications, and that this distinction was made difficult by the inconsistencies between product licensing and clinical guidelines (Fukada et al., 2012). Other contributors to this lack of clarity may be the differences in licensing between gabapentin and pregabalin, as well as between regions. Whilst pregabalin is not licensed for fibromyalgia in Europe, unlike the US, it is recommended by the European League Against Rheumatism (EULAR) (Macfarlane et al., 2017), and often features in the pharmacological repertoire used by clinicians in the UK (Public Health England, 2014). It is also likely that the lack of objective criteria for licensed and off-label uses such as neuropathic pain and fibromyalgia, respectively, allows for the expansion of their use to other conditions with common presenting symptoms, such as pain.

There is growing evidence that the use of the gabapentinoids in off-label painful conditions may be a large determinant in the increase of both gabapentin and pregabalin prescribing. Whilst a 2013 study of The Health Improvement Network (THIN), a UK primary care database, concluded that the majority of pregabalin use between 2004 and 2009 was for licensed indications, more than 60% of prescriptions were unattributable to licensed indications in their primary analysis. Their conclusion was most likely drawn from their sensitivity analyses, whereby they assumed that the pain of patients prescribed pregabalin

[2] Unlike in the UK, pregabalin is not licensed for peripheral neuropathic pain such as lumbar radiculopathy in Canada.

was neuropathic (Asomaning et al., 2016). A 2015 article analysing trends in UK primary care prescribing proposed that the increased prescribing of the gabapentinoids between 2004 and 2014 was "probably due to their use for pain" (Chaplin, 2015, p. 14). This is not only true of the UK, as in a recent editorial in the New England Journal of Medicine, Goodman and Brett (2017, p. 411) remarked that in both inpatient and outpatient settings in the US they had observed clinicians "increasingly prescribing gabapentin and pregabalin for almost any type of pain". A study of prescribing in Ontario, Canada, reported that greater than 80% of patients prescribed pregabalin between April 2013 and March 2014 had a diagnosis of a musculoskeletal condition. Although a smaller proportion of this group of patients had a musculoskeletal condition diagnosis without the presence of a neurological or fibromyalgia diagnosis (approximately 20%), the common use of NSAIDs and opioids in the year prior to first pregabalin prescription may point to the use of pregabalin in musculoskeletal conditions in which these medications are commonly used (Kwok et al., 2017). This may also reinforce the belief that the diagnoses of suspected fibromyalgia or neuropathic pain can be used for a large number of patients presenting with pain. A Spanish cross-sectional primary care study found that 45.2% of patients prescribed pregabalin had a diagnosis of bone and joint pain (Viñas-Bastart et al., 2017). Whilst this study did not specify conditions in this category, OA is likely to be the most prevalent. In summary, despite a substantial increase in gabapentinoid prescribing, and the growing consensus that they are being used for pain, an understanding of which conditions are contributing to this increase is lacking. This resulted in the development of the hypothesis that OA may be a contributor to this increase.

It is highly likely that the gabapentinoids are being used in patients with OA, largely due to the prevalence of the condition and common comorbidities. For instance diabetes is a

condition that more than 14% of sufferers of OA also experience (Louati et al., 2015). The resulting complication, diabetic neuropathy, is estimated to occur in roughly 21% of diabetic patients (Abbott et al., 2011). As a result, many patients would have a licensed indication for a gabapentinoid prescription. However, there is anecdotal evidence that the gabapentinoids may be being used ***for*** OA, rather than solely in patients with the condition. Goodman and Brett (2017, p. 412) also proposed in their editorial that clinicians in the US may use the fibromyalgia license of pregabalin to prescribe pregabalin off-label for "ill-defined pain… but also for more defined conditions such as low back pain and pain from osteoarthritis". However, as was illustrated in the opening chapter of this thesis, OA is not as clearly defined in practice as might be expected, but instead there exists a spectrum of severity which can result in a large variation in prevalence estimates. Within the UK, there is a belief that general practitioners may be willing to use these drugs in chronic joint pain (J Bedson, personal communication, 2017). The British Pain Society suggests that doctors prescribing a medication off-label for pain should "be satisfied that there is sufficient evidence… to show its safety and efficacy" and that the "reasons for the choice" of such a medication should be recorded (The British Pain Society, 2012, p. 8). As a result, further exploration of the rationale for the use of the gabapentinoids, as well as of the potential benefits and harms to patients prescribed a gabapentinoid, is required.

2.3 Possible Rationale for the Use of the Gabapentinoids in OA

There may be many reasons why gabapentin and pregabalin are being used for the pain experienced by patients with OA. Primarily among these are the concerns of the prescriber with current pharmacological options (with a lack of effective alternatives), the central

mechanisms involved in the pain of some patients with OA and the potential effects of illegal pharmaceutical marketing.

When gabapentin first entered the market in the US its manufacturer, Warner-Lambert, advertised its use for numerous non-licensed indications. These included bipolar disorder, migraine and pain (Kaufman, 2004; Petersen, 2008; Steinman et al., 2006). Although prescribing a medication for a non-licensed indication is legal, advertising is not, and a reported $430 million settlement was reached in the 2004 Franklin v Pfizer (who had since acquired Warner-Lambert) case (Department of Justice, 2004). Whilst the direct effect of this marketing strategy on the behaviour of clinicians is unknown, there may have been effects on the subsequent research, which could influence prescribing. There is evidence that industry-sponsored trials of the gabapentinoids in off-label conditions were not reported fully, or had altered primary outcomes, when the results were not significant (Vedula et al., 2009). This bias may have affected clinical practice as the 2010 NICE guidelines on neuropathic pain only included published studies, as highlighted by a response to an article summarising the recommendations (Tan et al., 2010). Advertising practices of pregabalin have also resulted in a lawsuit. In 2012 Pfizer were fined $2.3 billion for inappropriate advertising of pregabalin and three other medications up until 2009 (The New York Times, 2009).

The concerns, as mentioned in Chapter 1, of the clinician with current pharmacological options for OA pain management may also lead them to prescribe alternative medications, such as the gabapentinoids. In the US it has been hypothesised that clinicians may lower their threshold to prescribe the gabapentinoids to avoid the prescription of opioids, in response to concerns about their use and clinical guidelines recommending considerations of non-opioid treatments (Goodman & Brett, 2017). If concerns with the currently

recommended treatment options for OA are a contributing factor to the prescription of the gabapentinoids, any current use may be expected to increase alongside the growing number of patients with OA, unless changes are made to treatment guidelines.

Although the comorbidities of the patient may result in the gabapentinoids being indicated in patients with OA, they may also have other effects on prescribing behaviours. For example a doctor may have found their use in a patient with diabetic neuropathy significantly improved this patient's OA pain, and thus decided to use the drug for non-diabetic patients. It is likely that interviewing clinicians would be required to further appraise this.

Finally, central mechanisms involved in OA pain, as mentioned in Chapter 1, may also be a reason for the use of the gabapentinoids in patients with OA. Authors of a trial of pregabalin in OA patients suggested that the effectiveness of pregabalin in combination with an NSAID is due to both inflammatory and neuropathic pain components (Ohtori et al., 2013), and authors of another trial, who assessed the efficacy of pregabalin in hand OA due to possible central pain mechanisms, concluded that pregabalin may present a "realistic alternative to pain management in OA" (Sofat et al., 2017, p. 2448). It has been stated that when challenged with ineffective treatments, "physicians may try new approaches that have some theoretical basis" (Klein & Tabarrok, 2004, p. 61). Could this be the theoretical basis? Although questions remain regarding the presence of 'true', definitive, neuropathic pain in patients with OA, patients with evidence of central sensitisation may still experience benefit from the gabapentinoids due to their effects on α-δ-1 subunits in the spinal cord and at other sites in the nervous system (Stahl et al., 2013). Equally, the anxiolytic properties of the gabapentinoids may also contribute to a reduction in the pain experienced by some patients, irrespective of the presence of neuropathic pain.

In summary, whilst there may be numerous reasons for the use of the gabapentinoids in OA, including a lack of effective treatment options and potential central mechanisms in OA pain, definitive information regarding the rationale for the prescribing of gabapentinoids in patients with OA is lacking.

2.4 The Efficacy of the Gabapentinoids in Osteoarthritis

Whilst anecdotal evidence suggests that the gabapentinoids may be being used in patients with OA, there is limited efficacy of their use in the management of the condition. Trial data remain limited to several animal studies (Kim et al., 2011; Ogawa et al., 2016; Rahman et al., 2009), and four published human trials of pregabalin in OA (Filatova et al., 2018; Ohtori et al., 2013; Sofat et al., 2017; Wright et al., 2017). There remains a paucity of data studying gabapentin in both clinical trials and drug utilisation studies in the context of OA.

Prior to trials with human participants, literature focussed on the effect of the gabapentinoids in animal models of OA. Rahman et al. (2009) reported that pregabalin may be beneficial in OA as it inhibited neuronal responses in rats that had been injected with monoiodoacetate (MIA), a substance used to chemically induce rapid and extensive joint destruction. However, Thakur et al. (2012) noted that a dose of 2 milligrams (mg) of MIA, as used by Rahman et al., induced what appeared to be axonal injury, as well as the same level of cartilage disruption when induced at lower doses. As a result the medication trialled in certain animal models may prove effective due to its effect on the manifested neuropathic pain, rather than the induced OA. This is compounded by the fact that animal models, such as MIA-induced joint destruction, may not accurately represent the typical post-traumatic or spontaneous processes of OA in humans (Arendt-Nielsen, 2017).

Current research on the efficacy of the gabapentinoids in humans remains sparse, with only four small (n<100) registered trials published to date. In 2013 Ohtori et al. (2013) conducted a randomised controlled trial with 89 knee OA participants, who received either pregabalin (25mg daily), meloxicam (an NSAID; 10mg daily) or a combination regime of the two treatments. When in combination, both drugs were significantly more effective at lowering patients' pain than either drug as monotherapy at the conclusion of the four week trial. Although not compared with placebo, no significant difference was observed between the two drugs when used separately. However, their analysis was limited by low dosages, a small sample size and a short period of follow-up. Sofat et al. (2017) conducted their trial with 65 hand OA participants. The participants were randomised to pregabalin (150mg daily), duloxetine (30mg daily), or placebo. At thirteen weeks, pregabalin was significantly more effective than placebo on a Numerical Rating Scale (NRS) and two of the three domains of the Australian and Canadian Hand Osteoarthritis Index (AUSCAN) in both the intention-to-treat and per-protocol analyses. In comparison, duloxetine was only statistically more effective than placebo on the NRS of the per-protocol analysis. As highlighted by the authors, again this trial was limited by small group sizes, and the findings may not be applicable to other joints, for instance due to the differences in pain characteristics and structure of large weight-bearing joints such as the hip and knee. In contrast to these two trials in OA, Wright et al. (2017) conducted their trial on 90 patients with knee OA who were selected with characteristics of neuropathic pain. Neuropathic pain was identified based upon the presence of an elevated cold pain threshold and a painDETECT questionnaire (PD-Q) score of ≥13. It should be noted however that a PD-Q score of 13-18, according to the original creators of the questionnaire, represents an uncertain result, "i.e. a neuropathic pain component can be present" (Freynhagen et al., 2006, p. 1915). Upon the conclusion of their four week trial period pregabalin (titrated to

a maximum daily dose of 300mg) was associated with greater reductions in WOMAC and painDETECT scores, and an increase in pressure pain thresholds, compared to paracetamol (maximum daily dose: 4g). This conference abstract did not present mean differences or equivalent figures, instead solely p-values of significance. It should also be noted that four of the five authors of this abstract received 'grant/research support' from Pfizer. Most recently, a Russian team of researchers published a conference abstract of a trial of pregabalin in 60 female patients with knee OA. As with the trial conducted by Wright et al. (2017), all patients had a neuropathic pain component, detected using the Douleur Neuropathique 4 questionnaire. Upon conclusion of the trial at five weeks, both patients prescribed pregabalin (dose unknown) or pregabalin and aceclofenac (an NSAID), had a significant improvement in pain and function, assessed using the DN4 and painDETECT questionnaires as well as the WOMAC and a visual analogue scale. However, between-group outcomes were not reported, and as a result the individual effect of pregabalin's use in OA is unclear (Filatova et al., 2018).

In summary, whilst four trials have suggested a possible role for pregabalin as an analgesic in the management of OA, there is a lack of data from large trials with long periods of follow-up. As a reason for the use of the gabapentinoids in OA may be the suggested centralised pain mechanisms, their efficacy in neuropathic pain conditions requires further evaluation.

2.5 The Efficacy of the Gabapentinoids in Neuropathic Pain Conditions

As the gabapentinoids feature on national treatment guidelines for neuropathic pain conditions such as post-herpetic neuralgia and painful diabetic neuropathy, one could suspect there is favourable evidence for their use. Both have clear somatosensory lesions, and thus fulfil the latest criteria to be defined as neuropathic pain. A 2014 systematic review found that gabapentin 1800mg daily was effective in reducing patients' post-herpetic neuralgia pain (Fan et al., 2014), whilst a 2013 meta-analysis found that both gabapentin and pregabalin were superior compared to placebo at improving patients' diabetic neuropathy pain (defined as ≥50% reduction in pain), with odds ratios of 3.98 (95% CI: 2.29, 7.68) and 2.78 (95% CI: 1.72, 4.62), respectively (Rudroju et al., 2013). The latest Cochrane review for the use of gabapentin in neuropathic pain was published in 2017. They reported that gabapentin doses of 1800mg and 3600mg daily could provide meaningful benefit to certain patients, although roughly half of patients experienced no improvement (Wiffen et al., 2017).

Although Giladi et al. (2015) reported that the patient-perceived efficacy of pregabalin was not statistically different between licensed and unlicensed indications, it may be more relevant to assess the efficacy of the gabapentinoids in conditions that have no clear lesion, such as fibromyalgia and low back pain. A 2017 systematic review found that both gabapentin and pregabalin, when used in low back pain, were associated with a significant increase in risk of adverse effects, with very limited evidence of benefit (Shanthanna et al., 2017). In fibromyalgia, it is clear as of 2009 that the European Medicines Agency believed there was a lack of favourable evidence for the licensed use of pregabalin in fibromyalgia. More recently, a 2016 Cochrane review of pregabalin in patients with fibromyalgia found that although there may be some benefit compared to placebo, this occurred only in a small

number of patients (approximately 10% more than placebo) (Derry et al., 2016). The 2017 Cochrane review of gabapentin found that data available was limited and of poor quality, and as a result they had insufficient evidence to provide a conclusion regarding its potential benefit in patients with the condition (Cooper et al., 2017). In those patients that do experience some benefit, this may be due to the previously mentioned anxiolytic properties of the gabapentinoids. This may particularly be the case in patients with fibromyalgia, as the odds ratio of having any comorbid anxiety disorder has been reported to be more than six times that of those without the condition (Bernik et al., 2013).

In summary, there appears to be a greater body of evidence of the efficacy of the gabapentinoids in conditions where there is a clear lesion of the somatosensory system than in those without. However, this data predominantly comes from studies of two neuropathic pain conditions, painful diabetic neuropathy and post-herpetic neuralgia. As reported by the Cochrane review of gabapentin, evidence for other neuropathic pain conditions is limited (Wiffen et al., 2017), and in conditions with no clear somatosensory lesion, such as low back pain, the potential efficacy of the gabapentinoids occurs only in a small minority of patients, and rarely outweighs the risk of harm.

2.6 The Potential Risks of Gabapentinoid Use

Whilst there is limited evidence of benefit of the gabapentinoids, particularly beyond clearly defined neuropathic pain conditions, the prescribing of gabapentin and pregabalin for OA may not be without risk. These risks include adverse effects experienced by the patient, interactions with other medications regularly prescribed to patients with OA and the possibility for diversion and misuse, whereby the drugs are not used as they were intended at the time of prescription.

2.6.1 Adverse Effects

Information regarding the safety of the gabapentinoids is primarily based on trial data. A systematic review assessing the safety of anticonvulsants and antidepressants in painful diabetic neuropathy reported that, in trials, pregabalin resulted in more than three times the number of withdrawals than placebo. Although gabapentin also resulted in more withdrawals, this was not statistically significant, and gabapentin was viewed as the safest compared to the other antidepressants and anticonvulsants studied.[3] However, the authors noted that all studies were shorter than four months in duration, meaning safety beyond this point could not be evaluated (Rudroju et al., 2013). The better safety profile of gabapentin compared to pregabalin was also reported by a systematic review assessing the tolerability of 12 anti-epileptic drugs (Zaccara et al., 2017). In the Cochrane review of gabapentin in neuropathic pain, although there was no evidence gabapentin caused a higher rate of serious adverse events, there was high quality evidence that withdrawals arising due to adverse events were more common with gabapentin than with placebo. They

[3] Assessed medications: Amitriptyline, Duloxetine, Gabapentin, Pregabalin, Valproate, Venlafaxine, Placebo.

also reported that the risk ratio of any adverse effect, compared to those taking placebo, was 1.3 (95% CI: 1.2, 1.4). More than 10% of participants experienced dizziness, drowsiness or gait disturbance (Wiffen et al., 2017).

Perhaps due to their very similar mechanisms of action, the adverse effects associated with pregabalin use are very similar to those associated with gabapentin. Pfizer's Summary of Product Characteristics (SmPC) for pregabalin indicates that the most common adverse effects include dizziness, drowsiness, weight gain and peripheral oedema (Pfizer, 2016). Other adverse effects of the gabapentinoids that have been reported by trials include cognitive and visual disturbances (Shanthanna et al., 2017), nausea and dry mouth (Cappuzzo, 2009).

Giladi et al. (2015) assessed the safety of pregabalin using questionnaires in a population of current and former users of pregabalin. To reduce inaccurate recall, they excluded former users of pregabalin that had not used the drug in the previous 12 months. In their study 70% of responders reported adverse effects associated with the use of pregabalin, and 70% of former users stated these effects were the reason for them discontinuing their therapy regime. One patient discontinued pregabalin due to suicidal ideation, a clearly dangerous potential adverse effect, but one that is rarely mentioned in the trial data reviewed for this thesis.

The safety of the gabapentinoids was assessed in two of the human OA trials (Ohtori et al., 2013; Sofat et al., 2017). Although no adverse effects were reported by Ohtori et al. (2013), the study was only four weeks in length, and the 25mg dose used is far below the 150mg recommended by NICE for neuropathic pain, which, based on the presence of nerve damage in animal trials, was the rationale for them trialling pregabalin in patients with OA (National Institute for Health and Care Excellence, 2013). Whilst this may have reduced the

analgesic efficacy, it may also have reduced the number of adverse effects. The thirteen week trial in hand OA conducted by Sofat et al. (2017) was with a higher dose and they also reported that adverse event occurrences were no more likely with pregabalin than placebo. However, the long-term safety of gabapentinoid use in OA remains poorly understood.

Efforts have been made to reduce the incidence of adverse effects experienced by patients taking the gabapentinoids. In practice, NICE recommend that the dose of gabapentin and pregabalin be titrated slowly to desired levels (National Institute for Health and Care Excellence, 2013), whilst trials have assessed combination regimes that therefore require a lower dose (Senderovich & Jeyapragasan, 2018), or topical therapies, which tend to cause fewer central adverse effects (Martin et al., 2017).

2.6.2 Misuse Potential

Initially, it was thought that gabapentin and pregabalin had a low potential for misuse and addiction. In one of the earlier studies of gabapentin use, Hamer et al. (2002, p. 269) reported that it was "a treatment option that has relatively few serious side effects and drug interactions". However, in 2010, years after its release on the market, studies of the possible abuse potential of pregabalin emerged (Filipetto et al., 2010; Schwan et al., 2010). Since then, concerns that the gabapentinoids may have the potential to be used as drugs of abuse have grown, and there has been a growing body of evidence that the abuse of these drugs is becoming increasingly common and problematic (Chiappini & Schifano, 2016; Smith et al., 2012).

A 2017 systematic review of gabapentin and pregabalin misuse reported that among the general population, the abuse of the gabapentinoids was much lower than traditional drugs

of abuse, such as cannabis. However, among patients with substance use disorders, this risk was more comparable, as up to 68% of opioid misusers also misused pregabalin (Evoy et al., 2017). Furthermore, whilst another 2017 systematic review concluded that there was no convincing evidence that the gabapentinoids possess substantial addictive power, they also highlighted that the risk of misuse was highest in patients with a current or historic substance use disorder (Bonnet & Scherbaum, 2017). Another population at an increased risk of gabapentinoid misuse appears to be those in prisons. The rate of gabapentinoid prescribing in UK prisons has been reported to be almost double the rate of prescribing in the community. Whilst this could be due to differences in the prevalence of licensed indications in this population of patients, this seems unlikely, and 56.1% of prisoners prescribed a gabapentinoid had a history of substance misuse, again demonstrating that this group of patients are a high-risk group that are liable to misuse these medications (Farmer, 2013). There is also an increasing number of patients transitioning from a gabapentinoid to other dependence forming medications, such as z-drugs and benzodiazepines (Cartagena et al., 2017), suggesting that the gabapentinoids may act as gateway drugs to other illicit or prescribed medications.

Features of the gabapentinoids that may point to their possible dependence-forming nature include a tolerance necessitating increasing doses for the same effect (Bonnet & Scherbaum, 2017), and a withdrawal syndrome of symptoms such as sweating, fatigue, insomnia and diarrhoea (Chiappini & Schifano, 2016). Gabapentin has been referred to by drug users as a “cheap man’s high” (Smith et al., 2016, p. 9) and a ‘euphoria-like’ state has also been reported by patients (Evoy et al., 2017; Goodman & Brett, 2017). It is thought that the appeal of the gabapentinoids to prospective abusers includes their low cost, ease of procurement and a misunderstanding of their abuse potential by prescribers (Evoy et al.,

2017). In 2014 Public Health England did publish a report to highlight to prescribers the risks of the gabapentinoids (Public Health England, 2014). As well as highlighting the discrepancy in the number of gabapentinoids prescribed across regions of England, pointing to their potential misuse as this was not felt to be accounted for by differences in patient demographics, this document provided information to prescribers on tapering and reducing doses of the gabapentinoids to minimise dependence and stockpiling.

There has been an increasing body of evidence that a growing black market of the gabapentinoids has enabled their abuse by patients not initially prescribed them (Kapil et al., 2014; Schifano, 2014). As is the case with opioids (Han et al., 2017), studies of the misuse of the gabapentinoids have reported that many patients who abuse these medications do not directly receive them from a doctor. A survey of those that misuse the gabapentinoids, as well as the GABA analogue baclofen, found that whilst many obtained them from health services, a similar proportion received them from family or acquaintances, or via the internet. 36.8% of the population misusing one of these three medications acquired them from multiple sources (Kapil et al., 2014). In Germany, the majority of patients who tested positive for urinary traces of pregabalin at opioid abuse treatment programmes were not prescribed the medication (Lyndon et al., 2017). The concerns regarding the growing diversion of the gabapentinoids has resulted in many studies concluding that efforts are required to reduce the diversion of these medications (Kapil et al., 2014; Lyndon et al., 2017; Schifano, 2014).

A study estimating the lifetime prevalence of abuse of gabapentin and pregabalin amongst the UK population aged between 16 and 59 years found the prevalence to be 1.1% and 0.5% for gabapentin and pregabalin, respectively (Kapil et al., 2014). Although the proportion of gabapentin abusers may be higher, this may be due to the higher rate of

gabapentin prescribing as of the two gabapentinoids, drug abusers display a clear preference for pregabalin. Reasons for this may include the desired effects occurring quicker due to its bioavailability of ≥90%, irrespective of dose, and its quicker absorption, with maximum plasma concentrations reached within one hour, compared to the three or four taken with gabapentin (Bockbrader et al., 2010).

2.6.3 Gabapentinoid-Related Overdose

One can speculate that the documented increase in the misuse of the gabapentinoids may be a factor in the increasing number of gabapentinoid-related overdoses and deaths being reported by studies. Due to the aforementioned pharmacodynamics of pregabalin, it features much more commonly in both emergency departments and at post-mortem than gabapentin, again reflecting that it may be the more dangerous drug of abuse, or merely preferred by at-risk drug users. A study of a National Self-Harm Registry in Ireland reported that between 2007 and 2015, 2,115 (2.9%) of all intentional drug overdoses were due to the gabapentinoids, and 92% of these were due to pregabalin. Although gabapentinoid-related overdoses presented less frequently than the number of overdoses associated with other classes of medications, such as the analgesics, the proportion of all overdoses involving a gabapentinoid increased from 0.7% in 2007 to 5.5% in 2015 (Daly et al., 2017). The number of gabapentinoid-related deaths has also substantially increased. Within England and Wales in 2016, pregabalin was mentioned as a possible cause of death on 111 death certificates, compared to 59 with gabapentin, although it was prescribed much less frequently. This was an increase from four and eight, respectively, in 2012, a disproportionate increase compared to their growing prescribing rates (Figure 2.3). During the same period of time deaths related to tramadol increased from 175 to 184, and deaths

related to antidepressants decreased (Office for National Statistics, 2017a). It should be noted that the annual estimates of gabapentinoid-related deaths may be conservative, as UK coroners selectively screen for gabapentin and pregabalin due to cost or lack of accreditation (Nahar et al., 2017), and not every drug detected may be reported on the death certificate (Lyndon et al., 2017). The proportion of gabapentinoid-related deaths involving opioids may point to the dangers of concomitant use, as their use in combination can have synergistic effects on sedation and respiratory depression (Gomes et al., 2017). In 2015 79% of deaths registered in England and Wales involving a gabapentinoid also mentioned an opioid on the death certificate, and this rose to 89% in 2016 (Office for National Statistics, 2017b). Although this may be due to substance abusers commonly using multiple drugs simultaneously, it may also be due to the synergistic effects of the two substances leading to a higher risk of overdose. It should also be noted that the lack of an antidote for a gabapentinoid-related overdose, unlike for opioids, means that management is challenging (Bonnet & Scherbaum, 2017).

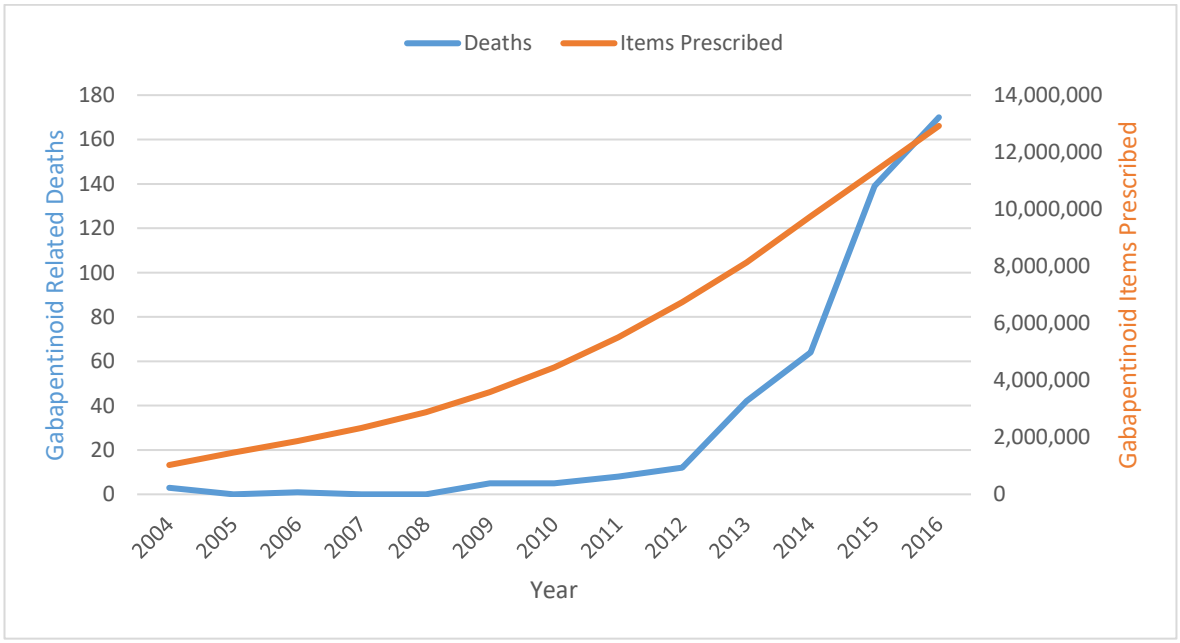


Figure 2.3 Comparison of Annual Gabapentinoid-Related Deaths and Number of Items Prescribed, in England and Wales (NHS Digital, 2017; Office for National Statistics, 2017a; Welsh Government, 2017)

2.6.4 The Potential Risks of Gabapentinoid Prescribing in the OA Population

Due to short, small trials, data related to the risks of gabapentinoid prescribing in the OA population are sparse. However, current knowledge can be applied to the large population of patients with the condition.

Firstly, adverse effects of gabapentinoid use may be particularly problematic in this population. Two common adverse effects, dizziness and drowsiness, may increase the risk of falls and lead to inactivity, respectively. As a risk factor for respiratory depression is increasing age, patients with OA may be at an increased risk of this severe adverse effect as a large proportion of the population of patients with OA is elderly (Gomes et al., 2017). The reporting by a pooled analysis of trials that euphoria occurred in 1.6% of patients prescribed pregabalin for peripheral neuropathic pain (Freynhagen et al., 2015), demonstrates that this adverse effect, which could potentially lead to misuse, may occur in the general population. The common use of opioids in patients with OA may also be a source for concern, not only due to the possible interaction, but due to patients becoming a source of diversion of both medications. Finally, as pain is a common motivation for patients to misuse opioids (Han et al., 2017), the nature of the condition may also be a risk factor for misuse, if reasons for misuse are similar between different medications.

As the majority of drug misusers tend to be younger than the average patient with OA, one could argue that this group would appear at low risk of the mentioned risks of misuse of the gabapentinoids. Indeed in 2016, the highest rates of drug misuse deaths in England and Wales for all substances occurred in those aged 40-49 years and this group, along with those aged 30-39 years, were also at highest risk of gabapentinoid-related deaths (Table 2.1). However, there were still many gabapentinoid-related deaths in the 50-69 years age group, when OA becomes more prevalent (Office for National Statistics, 2017c).

Table 2.1 Pregabalin and Gabapentin Deaths in 2016, by Sex and Age Group, with Corresponding Mortality Rates (Office for National Statistics, 2017c, 2017b)

Age Group	Deaths					Population Mid-2016	Deaths per 1,000,000 individuals
	Pregabalin		Gabapentin		*Total*		
	Males	Females	Males	Females			
≤20	0	1	0	0	1	13,812,700	0.1
20-29	6	1	3	1	11	7,783,500	1.4
30-39	31	13	8	5	57	7,664,600	7.4
40-49	28	9	9	9	55	7,812,600	7.0
50-69	14	8	12	11	45	14,019,800	3.2
≥70	0	0	0	1	1	7,288,000	0.1
Total	*79*	*32*	*32*	*27*	*170*	*58,381,200*	*2.9*
	111		*59*				

The high prevalence of OA may also be problematic, as even a small proportion of patients prescribed a gabapentinoid will result in many prescriptions being issued. Whilst the risk of misuse may be relatively low in the general population compared to high risk groups such as those with a history of substance use disorder, this increased community prescribing may be problematic as a recent research report published in Addiction demonstrated a strong correlation between the number of gabapentinoid prescriptions issued and related deaths. For every 100,000 prescriptions in England and Wales, deaths increased by 5% (Lyndon et al., 2017).

2.6.5 Summary of the Potential Risks of Gabapentinoid Use

There are growing concerns with the increasing use of the gabapentinoids, in particular with regards to their possible diversion and potential for misuse, resulting in an increasing number of gabapentinoid-related deaths. In light of this, the Advisory Council on the Misuse of Drugs recommended to the UK government in January 2016 that the gabapentinoids be classified as Class C medications under the Misuse of Drugs Act 1971

(Advisory Council on the Misuse of Drugs, 2016). During 2017 the British Medical Association also called for them to become controlled medications. The UK government have accepted this proposal, pending a consultation assessing the effect the reclassification would have on the healthcare sector (Iacobucci, 2017). Opinion is that this implementation of Class C status on gabapentinoid prescribing is likely, and there are three potential outcomes of this legislation. One is that gabapentin and pregabalin be controlled as Schedule 3 medications according to the Misuse of Drug Regulations 2001, as well as being required to be stored securely. Implications of this control would include the requirement of a 'wet' signature for each gabapentinoid prescription. The second option is the same as option one but does not require safe custody of gabapentin and pregabalin. Whilst this is not as stringent, it is believed that the required regular auditing of gabapentinoid prescribing would prevent diversion. The last option is that pregabalin and gabapentin are controlled within Part 1 of Schedule 4. Although this would provide similar benefits to option two, the same safeguards against diversion would not be provided (Home Office, 2017).

2.7 Conclusion and Study Aims

Prescriptions of the gabapentinoids gabapentin and pregabalin have risen sharply in recent years. Due to the large number of patients with OA and the prevalence of comorbidities that are licensed indications of the gabapentinoids, it is likely that the gabapentinoids are being used in this population of patients. However, anecdotal evidence both in the UK and US suggests that the gabapentinoids may be being used off-label specifically for the patient's OA pain. Possible reasons for this off-label use include concerns with the current pharmacological options for the treatment of OA, a potential neuropathic component to

the pain experienced by some patients with the condition and illegal marketing. As suggested by the British Pain Society, use of off-label medications for painful conditions should offer the "best balance of benefit against harm for any given patient" (The British Pain Society, 2012, p. 11). With only four small trials to date, data of efficacy remain sparse. On the contrary, the risk of adverse effects, diversion and misuse are increasingly being reported. As a common painful condition such as OA could contribute to this increased prescribing and risk to patients, further research is warranted.

As a result, the aim of the research in this thesis is to explore the trends over time in incident gabapentinoid prescribing in patients with OA. The Clinical Practice Research Datalink (CPRD) will be used to provide an understanding of whether the risk of patients with OA receiving a gabapentinoid has increased, and which patients with OA are most likely to receive a gabapentinoid prescription. This will be achieved by stratification of the incidence rate of gabapentinoid prescribing by calendar year, as well as by a patient's gender, age, geographical region and time since diagnosis. As the rationale for the use of the gabapentinoids in patients with OA is not well understood, an attribution analysis will be performed to explore whether OA, or other comorbidities, are responsible for the observed increase in gabapentinoid prescribing.

3 Methods

As demonstrated by the background chapters, literature suggests that the gabapentinoids (gabapentin and pregabalin) may be increasingly being used as analgesics in painful conditions. The proportion of this use that is off-label, beyond the licensed indication of neuropathic pain, is poorly understood. There is anecdotal evidence to suggest that the gabapentinoids may be being used for the pain experienced by patients with OA, a common cause of pain in older adults. However, use of these drugs may be problematic. The analysis within this thesis will therefore ascertain the incidence rate of gabapentinoid prescribing in patients with OA. To provide a better understanding of the proportion of patients with OA who may be prescribed a gabapentinoid for this common, painful condition, the study will also attempt to identify those patients with no other licensed or unlicensed indication for the gabapentinoids, where pain associated with OA may be the indication for prescribing.

3.1 Choice of Data Source

There were several possible sources of data to analyse gabapentinoid prescribing in patients with OA. Whilst information gathering would have been possible by surveying patients with OA, or interviewing doctors about their prescribing behaviour, anonymised electronic health record data offered several advantages. Firstly, as the majority of OA care is provided by general practitioners within the UK, primary care electronic health records provide prospectively-gathered information of a patient's OA consultations and

gabapentinoid prescriptions. These data points allow for both the construction of a cohort of patients who are diagnosed with OA and the estimation of the frequency of gabapentinoid prescribing in these patients. Secondly, as 90% of NHS consultations occur within primary care (Gregory, 2009), primary care data is a rich source of information, both in terms of the number of patients and length of follow-up. As a result, incidence rates could be estimated with an acceptable level of precision, even after stratification. Finally, the use of electronic health records was a time efficient and cost effective approach that did not require a new Health Research Authority application and approval. In summary, the use of electronic health records was thought to be an efficient, powerful and reliable source of data for this study's research objectives.

3.2 Primary Care Electronic Health Records

There are currently five large UK primary care datasets available: The Clinical Practice Research Datalink (CPRD), QResearch, ResearchOne, The Health Improvement Network (THIN), and the Royal College of General Practitioner's Research and Surveillance Centre (RSC). Whilst the different databases may compile information from different software packages used by general practices, all have a similar structure.

3.2.1 Structure of Electronic Health Records within the United Kingdom

Within the UK, primary care information is currently recorded using the hierarchical Read code system (NHS Digital, 2018), which was developed by Dr James Read in the 1980s (Benson, 2012). As well as patient demographics, Read codes are recorded for many

patient-related data points that occur in the practice, including diagnoses, symptoms and signs, prescriptions and immunisations (Herrett et al., 2015).

Data can be inputted by general practitioners (GPs) as well as by other practice staff. Other staff may include both clinicians, such as nurses or physiotherapists, and non-clinicians, such as receptionists or other administrative staff. The proportion of data inputted by non-GP staff is increasing. A study of QResearch revealed that of healthcare professionals, GPs entered 61.9% of Read codes in the financial year 2007/2008, a decrease from 75.7% in 1995/1996. The remaining data were inputted by nurses or other clinical staff (34.5% and 3.7% in 2007/2008, respectively) (Hippisley-Cox & Vinogradova, 2009).

A patient's primary care health records may also include data from other healthcare institutions. Such institutions that may diagnose conditions or prescribe medications in the UK include walk-in centres, accident and emergency departments, hospitals and mental health centres, as well as providers of private medical care. Information from the above institutions will still feature within a patient's primary care records providing data from communicating letters received by the general practice are uploaded and recorded appropriately.

For the purpose of this thesis, the Clinical Practice Research Datalink (CPRD) was chosen for several reasons. Firstly, compared to the other primary care electronic health record databases, the CPRD is by far the most frequently used in published studies (Mannan et al., 2017). It has also been validated for a number of diagnoses, including musculoskeletal and connective tissue disorders (Herrett et al., 2010; Williams et al., 2012). Finally, the CPRD was chosen for convenience and efficiency - the Institute for Primary Care and Health Sciences at Keele University already held a CPRD GOLD license, and extensive experience of the dataset, in the form of prior analysis and publications, was readily available.

3.2.2 The Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD) is an electronic primary care database overseen by the Medicines and Healthcare Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR). It is a database of anonymised data, first collected in 1987, which is uploaded monthly from participating general practices who are trained to record information appropriately using the Read code hierarchy. As of 2018 there are two datasets offered by the CPRD: CPRD GOLD and CPRD AURUM. CPRD GOLD comprises data from practices recording information using the VISION software system. CPRD AURUM is a separate database of data from practices using Egton Medical Information Systems (EMIS). Although they offer similar information, due to slight differences in coding and structure they are offered as two distinct datasets (CPRD, 2018).

Prior to 2012, the CPRD included only primary care information and was known as the General Practice Research Datalink (GPRD). Since then, the incorporation of linked data allows patient information from primary care to be linked to other sources, such as Hospital Episode Statistics, as well as to death and cancer registries (provided by the Office for National Statistics and Public Health England, respectively). To ensure anonymity of patients, the linkage process is undertaken by the CPRD team before the linked data is released to researchers (CPRD, 2018).

In June 2017 a Primary Care Working Group Datasets Project released information about several datasets, including CPRD GOLD. At this time there were 693 practices contributing data of 14.2 million patients to the CPRD, of which 2.8 million were active (The Farr Institute, 2017). The CPRD has been shown to be representative of the UK population. Potentially due to 98% of the UK population being registered with a general practice in 2013, the patients within the CPRD at this time were representative of the 2011 UK census

according to age, sex, and ethnicity (Herrett et al., 2015). Coding of ethnicity was historically poor but has improved since its introduction in the Quality and Outcomes Framework (QOF) in 2006 (Mathur et al., 2014). Other studies of the CPRD have demonstrated that compared to the UK population, patients who do consult tend to be older, female and from areas of higher deprivation (Hobbs et al., 2016; Mukhtar et al., 2018).

The CPRD GOLD dataset was chosen as the Institute at Keele University already held a license. Permission was sought to use the GOLD dataset by completion of an application form (Protocol 18_007, available in Appendix 1.1 on page 158), submitted to the Independent Scientific Advisory Committee (ISAC) in December 2017. This application was approved in April 2018, following protocol clarification and amendments. No further ethical permission, such as that needed when gaining information from patients via questionnaires, was required due to the nature of the descriptive research performed on the anonymised data.

3.3 Study Design

This study analysed prospectively-collected data from a cohort of patients in the CPRD. To analyse prescription rates in patients with OA using a denominator of person-time, and to thus ascertain an accurate period of follow-up, the date of initial diagnosis of OA (i.e. incident cases), was used as a patient's entry into the cohort. From this date onwards however patients could reconsult for OA, and could thus be viewed as 'prevalent' cases. The date of initial OA consultation was chosen as it was a clear starting point to the follow-

up of patients who definitely had the condition prior to receiving a gabapentinoid prescription.

The study period during which a patient could be recruited into the cohort ran from the 1st January 1995 to the 31st December 2015. Whilst the starting year of 1995 predates the likely use of the gabapentinoids, it allowed the identification of gabapentinoid prescriptions in patients who received their initial OA diagnosis several years before.

3.3.1 Population

All objectives below were analysed from the same cohort of patients with OA. The population used in this cohort were patients in the CPRD who were newly diagnosed with OA during the study period. In terms of Read codes, a patient's initial diagnosis of OA may be coded no differently from follow-up appointments. As a result, identification of only those with a new OA diagnosis required the exclusion of prevalent consulters. Patients with prevalent disease were determined by identifying their first consultation for OA during the study period, and excluding those with a consultation within the three years prior to this date (Figure 3.1). Patients who had received a knee or hip arthroplasty, a common end point for patients with OA, during this three year period were also excluded. Read codes for joint arthroplasty, which can be found in Appendix 2.3 on page 182, were already held by the research institute, having been used in a prior CPRD ISAC protocol (ISAC 15_211).

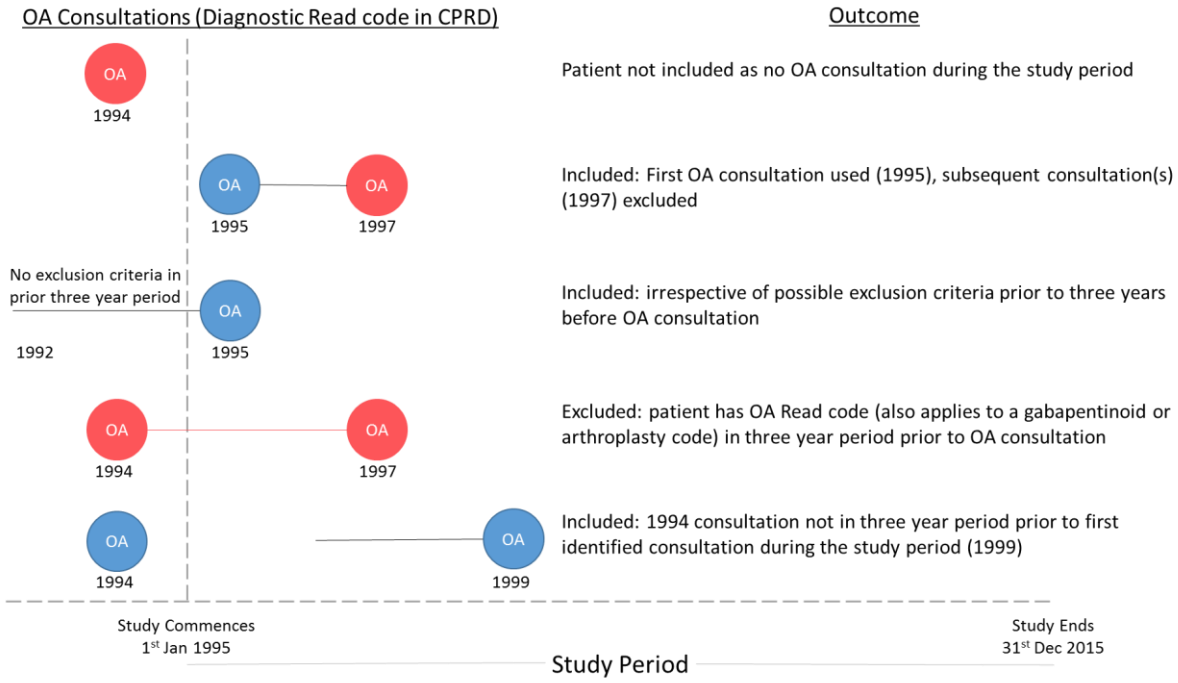


Figure 3.1 Scenarios of the Inclusion (Blue) and Exclusion (Red) of Patients, Based on the Year of their OA Consultation

The three year period prior to OA diagnosis was chosen as this has been shown to effectively exclude the vast majority of prevalent consulters with the condition (Yu et al., 2015). Other criteria had to be fulfilled for a patient to be included in the study cohort (Figure 3.2). To establish temporality between exposure and outcome, and to ensure the diagnosis of OA preceded the prescription of a gabapentinoid, patients with a gabapentinoid prescription in the three years prior to their first OA diagnostic consultation were excluded. The patient also had to be aged 40 years or over on the date of this first consultation as used by prior studies of OA (Ho-Pham et al., 2014; Prieto-Alhambra et al., 2014; Thiem et al., 2013). At the practice level, data uploaded had to be 'up to standard' (UTS) during the three years prior to, and the follow-up period since, diagnosis. UTS is a measure provided by the CPRD and whilst not a definite indicator of data quality, the CPRD recommends that it be used as a measure to select "research-quality patients and periods of quality data recording" (Herrett et al., 2015, p. 832).

3.3.2 Definition of Incident OA

The case definition of incident OA, used as the cohort member's index date, was the first occurrence within the study period of a definitive, diagnostic OA Read code in their health records. This approach has been used (Turkiewicz et al., 2014; Yu et al., 2017) and validated (Lix et al., 2006) by prior studies. This definition also rarely (1.3%) results in a different diagnosis (Prieto-Alhambra et al., 2014). The list of Read codes used for this definition of OA was taken from established code lists held by the research institute (available from www.keele.ac.uk/mrr). This code list has been used in prior research of the CPRD (Yu et al., 2017 [ISAC 14_090]), and can be found in Appendix 2.1 (page 175). The requirement of a definitive OA diagnostic Read code is a relatively specific definition of OA, as many patients presenting to primary care with symptomatic OA may be managed under non-specific 'clinical OA' Read codes (Jordan et al., 2014). The decision was made to use the specific definition, instead of the more sensitive 'clinical OA', primarily to provide a greater understanding of the attribution of a gabapentinoid to OA or other conditions. The use of 'clinical OA' Read codes, such as 'joint pain', may have made it more challenging to distinguish OA from other common causes of pain and potential gabapentinoid indications, such as fibromyalgia.

3.3.3 Censoring of Patients

The follow-up of a patient came to an end on the date of their first censoring event. Possible censoring events were a patient receiving their first gabapentinoid prescription, transferring out of their GP practice, dying, or reaching the study end date (31st December 2015). Follow-up also came to an end if the GP practice chose to no longer upload data to the CPRD. In the instance that a patient received their first gabapentinoid prescription on

the same date as another censoring event, the gabapentinoid prescription took priority, and was counted in the analysis.

Details of the criteria of a patient's index and censoring dates are displayed in Figure 3.2.

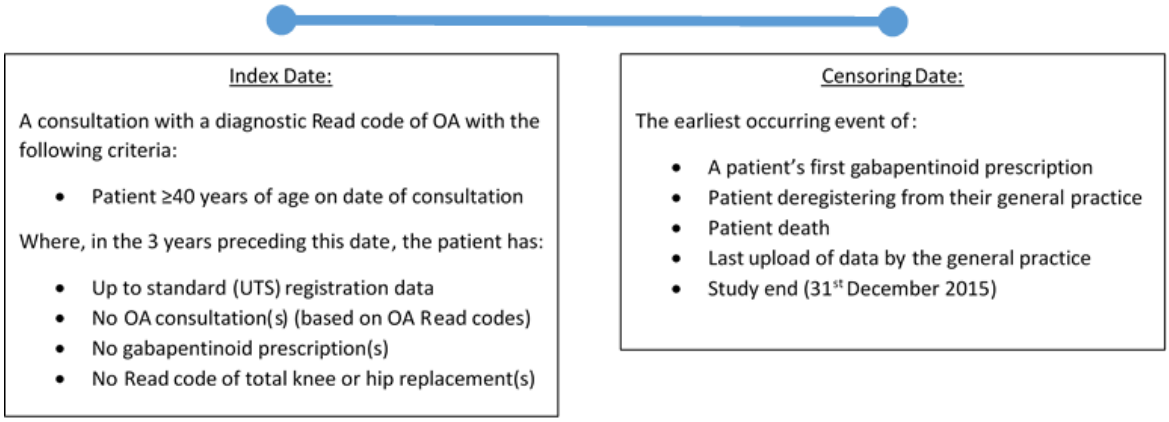


Figure 3.2 Criteria of Index and Censoring Dates for Cohort Members (OA: osteoarthritis)

3.3.4 Gabapentinoid Prescriptions

Prescriptions are recorded in the CPRD as product codes. The code list of product codes used (presented in Appendix 2.2, page 178) was derived from a recent report on Dependence Forming Medications that included the gabapentinoids (Cartagena et al., 2017). This was compared with code lists available online in the clinical codes repository (ClinicalCodes.org), provided by the University of Manchester (University of Manchester, 2018).

3.3.5 Possible Indications for Gabapentinoid Prescriptions

Due to the structure of electronic primary care records, it is not possible to directly link a prescription to an indication or diagnosis. Whilst every cohort member had received a diagnosis of OA, it is possible that a gabapentinoid prescribed to a member of this cohort was due to a comorbidity. As a result, possible indications were identified.

As shown in Table 3.1, identified licensed indications of the gabapentinoids included epilepsy, generalised anxiety disorder (for pregabalin), and neuropathic pain. These conditions were identified using NICE guidelines and the BNF. Possible unlicensed indications of the gabapentinoids were identified using the BNF (Joint Formulary Committee, 2018) and by literature searches (Cartagena et al., 2017; Fukada et al., 2012; Mack, 2003; Wallach & Ross, 2018). Read code lists for the identified comorbidities were established using publically available code lists sourced from the University of Manchester's repository (University of Manchester, 2018), as well as by searching the CPRD bibliography available online (methods and articles used specific to each condition are also available in Table 3.1). Codes were verified using the CPRD Code Browser (Version 3.0.0, copyright © 2012-2018 of Clinical Practice Research Datalink Medicines and Healthcare Products Regulatory Agency) and the NHS Clinical Terminology Browser (Version 1.04) was also used to detect any missing codes. Read codes for these conditions, available in Appendix 2.4 (page 184), were checked by two senior clinicians: JB, a senior academic general practitioner and JA, an academic consultant in pain management.

Table 3.1 Identified Licensed and Unlicensed Indications of the Gabapentinoids and the Sources Used in Code List Development

Condition	Source of Code List
Licensed	
Epilepsy	ClinicalCodes.org[4]
GAD[5]	NHS Browser, ClinicalCodes.org[6]
Neuropathic Pain	CPRD Bibliography[7], NHS Browser, ClinicalCodes.org[8]
Unlicensed	
Alcohol Withdrawal	ClinicalCodes.org[9]
Attention Deficit Disorder	CPRD Bibliography[10], NHS Browser
Bipolar Disorder	ClinicalCodes.org[11]
CRPS[12]	NHS Browser
Fibromyalgia[13]	CPRD Bibliography[14]
Menopausal Hot Flushes[15]	NHS Browser
Migraine[15]	ClinicalCodes.org[16]
Panic Disorder	ClinicalCodes.org[17]
Restless Legs Syndrome[18]	CPRD Bibliography[19], NHS Browser

GAD: generalised anxiety disorder; CRPS: complex regional pain syndrome

[4] (Gorton et al., 2018; Horsfield, 2005; Kontopantelis et al., 2015).
[5] Generalised anxiety disorder is an indication for pregabalin only (Joint Formulary Committee, 2018).
[6] (Windfuhr et al., 2016).
[7] (Berger et al., 2012; Hall et al., 2013).
[8] (Fairhurst et al., 2016; Gorton et al., 2018; Horsfield, 2005; Khan et al., 2010; Kontopantelis et al., 2015; Zhong et al., 2018).
[9] (Doyle et al., 2016; Thompson et al., 2017).
[10] (Newlove-Delgado et al., 2018).
[11] (Windfuhr et al., 2016).
[12] Complex regional pain syndrome has two subtypes. Type 1 has no nerve lesion, and the syndrome was deemed non-neuropathic by a 2010 review (Naleschinski & Baron, 2010).
[13] Fibromyalgia is not a licensed indication within the UK, although is a licensed indication of pregabalin in the US and is seen as part of the repertoire for treatment within Europe (Public Health England, 2014).
[14] (Collin et al., 2017).
[15] Menopausal hot flushes and migraine are listed as indications of gabapentin by the BNF as of May 2018, but were not licensed during the study period (Joint Formulary Committee, 2018).
[16] (Gorton et al., 2018).
[17] (Windfuhr et al., 2016).
[18] Restless legs syndrome is not a licensed indication of gabapentin or pregabalin, but is a licensed indication of gabapentin enacarbil, the prodrug formulation (not analysed in this thesis).
[19] (Van De Vijver et al., 2004).

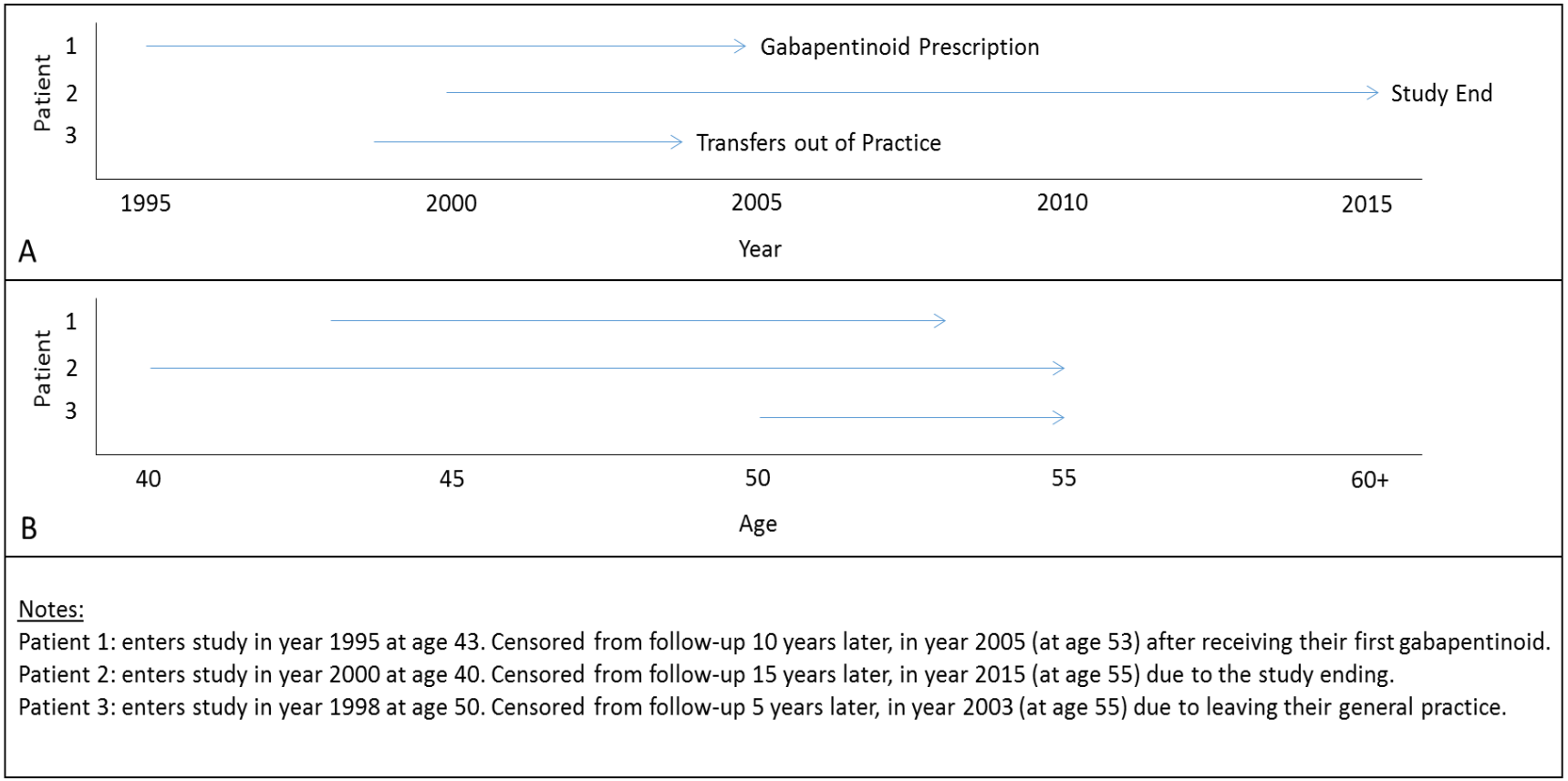
3.4 Statistical Analyses

This thesis includes descriptive analyses of the CPRD as well as estimations of rates, absolute rate differences, and rate ratios. All analyses were performed using IBM SPSS Statistics version 24.

3.4.1 Objective 1: Incidence Rate of Gabapentinoid Prescribing in OA

Objective 1 was to estimate the incidence rates of first gabapentinoid prescriptions in patients newly diagnosed with OA during the study period (1st January 1995 to 31st December 2015). Lexis expansion was used to estimate incidence rates along three different time axes: calendar year, a patient's attained age, and time since index OA diagnosis. Attained age, used by prior studies of OA (Turkiewicz et al., 2016), was felt to provide a more relevant measure of age for the clinical decision to prescribe a gabapentinoid than age on the date of index OA diagnosis. The use of Lexis expansion allowed for the analysis of two or more time-dependent variables simultaneously (for instance calendar year and age, as demonstrated by Figure 3.3 and Figure 3.4), permitting the exploration of changing age as a confounding variable in the analysis of gabapentinoid prescribing over the course of the study period (Nitika et al., 2017). Time since index date can also be calculated using this method. However, this was not a key feature of the analysis in this thesis as the index date of diagnosis of OA is dependent on the definition of OA used, and as such the date of initial consultation can be viewed merely as an arbitrary time point at which follow-up within this cohort began. This is further discussed in Chapter 6.

In this incidence analysis the numerator was the number of first gabapentinoid prescriptions occurring in the calendar year of interest. The denominator was the number of person-years contributed by cohort members in that year. Incidence rates throughout this thesis are presented as first gabapentinoid prescriptions per 1,000 person-years, and 95% confidence intervals (CI) for incidence rates were calculated using a publicly available online Poisson regression calculator (Dean & Sullivan, 2018). Due to the anticipation of small cell sizes, particularly when stratified by calendar year, age was stratified into 10 year age groups (40-49, 50-59, 60-69, 70-79 and 80+ years). A patient's age at index and at censoring was calculated based on their year of birth, the level of precision provided by the CPRD. The crude annual incidence rates were then age-standardised using direct standardisation (Naing, 2000). As the population of cohort members used in this study were those with an OA diagnosis based on the presence of a diagnostic Read code in their medical records, the reference population used for direct age-standardisation was cohort members present in mid-2015 of this study. The 30th June was used as the mid-year date, as this date is used by the Office for National Statistics for their mid-year population data (Office for National Statistics, 2018).



Notes:
Patient 1: enters study in year 1995 at age 43. Censored from follow-up 10 years later, in year 2005 (at age 53) after receiving their first gabapentinoid.
Patient 2: enters study in year 2000 at age 40. Censored from follow-up 15 years later, in year 2015 (at age 55) due to the study ending.
Patient 3: enters study in year 1998 at age 50. Censored from follow-up 5 years later, in year 2003 (at age 55) due to leaving their general practice.

Figure 3.3 Cohort of Three Patients Analysed by (A) Calendar Year, and (B) Age.

N.B. the age at censoring (attained age) has been used in the analysis

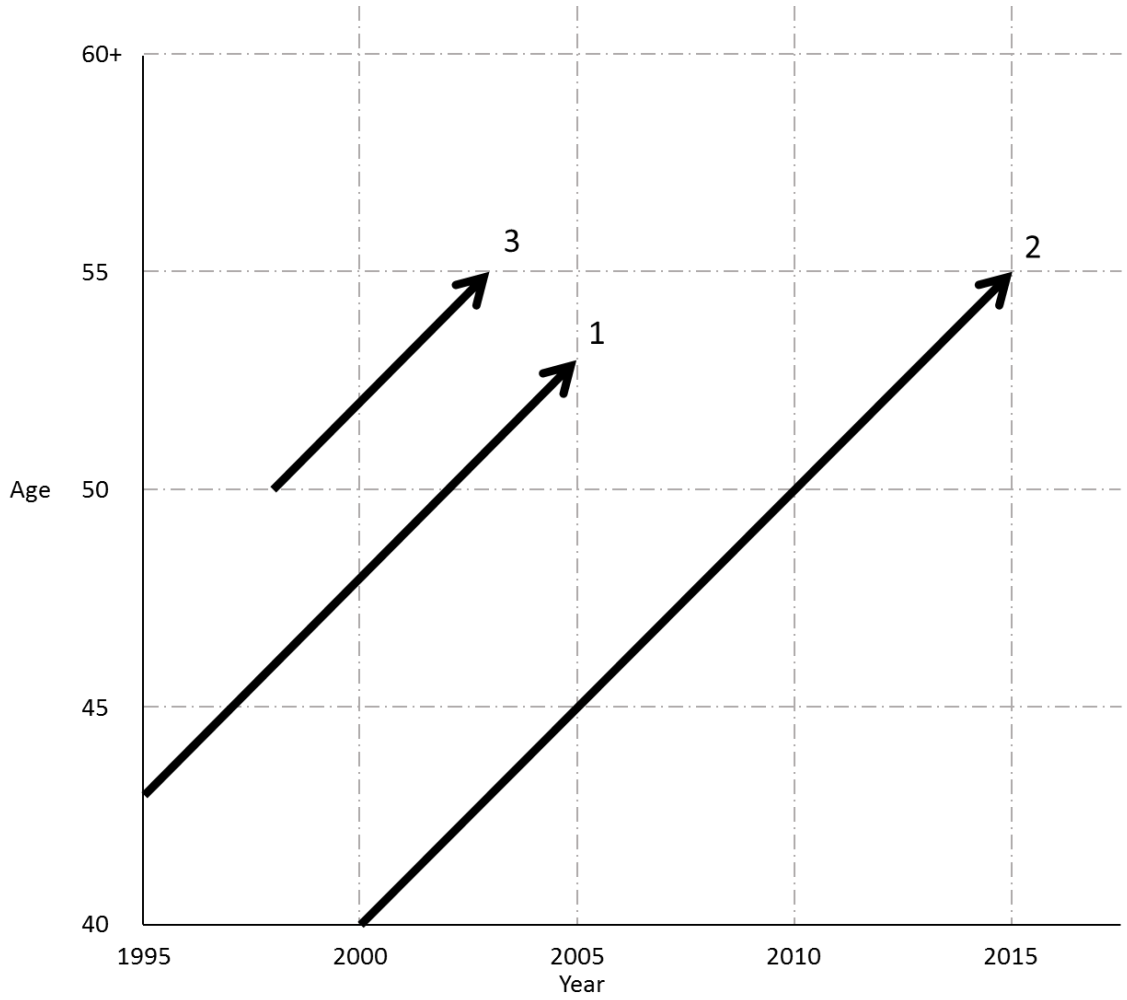


Figure 3.4 Lexis Expansion of Cohort from Figure 3.3, Demonstrating the Analysis of Calendar Year and Age Simultaneously

3.4.2 Objective 2: Stratification of Incidence Rates

Objective 2 stratified the incidence rates of gabapentinoid prescribing found in Objective 1 by patient gender, geographical region and time since index OA diagnosis. Geographical region is stratified into 13 regions and is provided by the CPRD, based on the location of the GP practice to which the patient is registered. Time since OA diagnosis was calculated from a patient's index date (their first OA consultation) until their time of censoring and was stratified into five-year age bands (<5, 5-9, 10-14, >15 years). The product codes of the gabapentinoids, provided by the CPRD, were used to identify the respective proportions of prescribing due to gabapentin and to pregabalin.

3.4.3 Objective 3: Attributing Prescriptions to OA and Licensed or Unlicensed Indications

As previously mentioned, one limitation of the CPRD and other similar databases in pharmacoepidemiology studies is the inability to link a prescription directly to a specific indication. As a result, although prescriptions of gabapentinoids may occur in patients with OA, it is not possible to directly link this prescription to their OA, and the prescriptions could therefore be issued for a comorbid condition (either a licensed or recognised off-label indication for the gabapentinoids). The primary attribution analysis explored the proportion of patients with a first gabapentinoid prescription that had a diagnostic Read code of OA during the period from 14 days before to 90 days after (inclusive) the date at which the gabapentinoid was issued.[20] This time window has been used in a previous study of the CPRD to identify musculoskeletal conditions in patients prescribed opioids (Bedson et al., 2016). Performing this attribution analysis within the time window around only the first gabapentinoid prescription, rather than including any subsequent prescriptions, may present less opportunities to assess the presence of diagnostic codes. However, this technique has been used in a prior study of pregabalin prescribing within the UK (Asomaning et al., 2016), and as the first prescription of a gabapentinoid would constitute a change in a patient's management, this prescription, more so than any other, should be accompanied by a diagnostic Read code for the relevant indication (Lawson et al., 1998).

To gain an understanding of the proportion of gabapentinoid prescriptions issued to patients with OA that may be due to a comorbidity, the presence of licensed and unlicensed indications (as displayed in Table 3.1 on page 69) were also assessed during this same time period. The primary analysis could therefore provide an estimate of the proportion of prescriptions attributable to OA as well as to other licensed and unlicensed indications. As

[20] This date may or may not have been a patient's first consultation of OA (i.e. their index date).

a result, the number of prescriptions unattributed to OA or the other identified indications could also be reported.

As the consultation closest to the gabapentinoid prescription was chosen for each condition analysed, cohort members could only have one consultation date for OA as well as for the licensed or unlicensed indications. However, patients could have Read codes within the same time window for more than one condition. As a cohort member with OA around the time of their gabapentinoid prescription may also have had a licensed or unlicensed indication present in their electronic healthcare records, the identified proportion of patients with a prescription attributable to OA may overstate the role of the condition in the prescribing of a gabapentinoid in this cohort of patients. As a result, the proportion of patients with OA in their electronic healthcare records at the time of prescription, but with no presence of a licensed or unlicensed indication, was also explored. In other words, attribution to a licensed or unlicensed indication took precedence over OA, to provide a more conservative estimate. Within this analysis no priority was given between licensed or unlicensed indications, and as such this thesis presents the proportion of patients with first gabapentinoid prescriptions attributable to OA (irrespective of other indications), to licensed or unlicensed indications, as well as those prescriptions in patients with a Read code for OA but with no evidence of a licensed or unlicensed indication.

The proportions of first gabapentinoid prescriptions attributed to OA or licensed and unlicensed conditions, as well as those prescriptions which remained unattributed, were stratified by patient age, gender and geographical region. The attribution of first gabapentinoid prescriptions was also stratified by calendar year and whether the prescribed gabapentinoid was gabapentin or pregabalin.

As the 105-day window (referred to in Chapter 5 as Window 1) surrounding the prescription date relies on the assumption that coding will be present at this time, the estimated proportion of first prescriptions attributable to OA may be conservative. Equally, as the presence of the Read codes for the licensed and unlicensed indications within this narrow time window may also be low, the proportion of first prescriptions that remains unattributed may be the upper estimate of the proportion of patients with OA prescribed a gabapentinoid with no indication. As a result sensitivity analyses, using the same technique, were undertaken to explore the effect of expanding the time period studied around the first prescription date (Figure 3.5). As in Window 1, the patient's nearest consultation date (based on the presence of a Read code) to their gabapentinoid prescription was used and as a result those first prescriptions attributed in the narrow time window were also attributed in subsequent analyses. The order of precedence, whereby licensed or unlicensed indications took priority over OA to provide a more conservative estimate of attribution, was also used in the sensitivity analyses. Window 2 analysed the proportion of patients with an OA or licensed or unlicensed indication Read code within six months before to six months after the date of their first gabapentinoid. Window 3 further expanded upon window 2, by assessing a further six months before the gabapentinoid date. Finally, the extreme was window 4, where first prescriptions were attributed based upon the presence of a Read code in the period from one year prior to their initial OA consultation to six months following their gabapentinoid prescription. The time frame of six months following the first prescription was also used by a previous study of pregabalin prescribing in primary care (Asomaning et al., 2016). As in Objectives 1 and 2, as well as in the primary attribution analysis, all attributed and unattributed prescriptions in the sensitivity analyses were stratified by a patient's age, gender and region, as well as by calendar year.

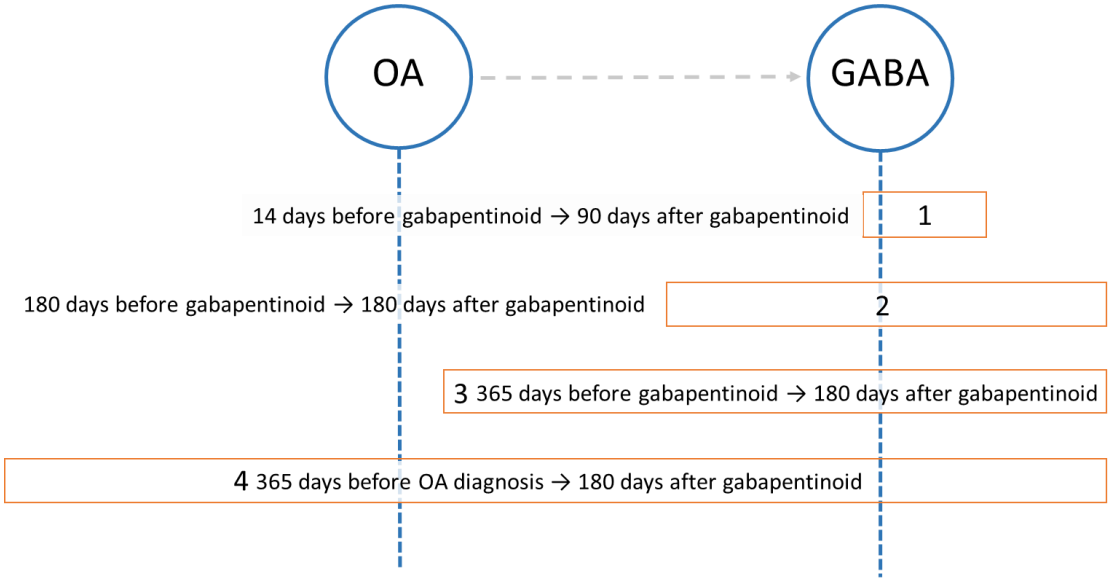


Figure 3.5 Time Periods Used in Attribution Analysis

3.5 Summary

The analyses in this study were designed to estimate the trends, by calendar year and patient age, in the incidence of first gabapentinoid prescriptions issued to members of a fixed cohort. Members of this study were UK patients aged 40 years and over newly diagnosed with OA between 1995 and 2015. Stratified analyses sought to further explore differences in the incidence of gabapentinoid prescribing among patients with OA, between men and women, as well as by geographical region. The above estimates describe the incidence of gabapentinoid prescribing *in* patients with a diagnosis of OA. Attribution analyses are then intended to allow the assessment of the proportion of OA patients prescribed a gabapentinoid *for* OA, as well as for comorbidities, including both licensed indications and other recognised off-label uses.

4 Results I

4.1 Cohort Characteristics

During the study period starting 1st January 1995 and ending 31st December 2015 there were 383,680 patients in the CPRD who were newly diagnosed with osteoarthritis (OA). Of these, 234,159 (61.0%) were female. Median age at first OA consultation was 66.0 years (IQR: 57.0, 75.0; range: 40, 107 years). The number of newly diagnosed cases of OA in each calendar year is shown in Figure 4.1, ranging from a minimum of 7,712 diagnoses in 1995 to a maximum of 26,072 in 2005. Throughout the study period there was an annual average of 108,106 person-years contributed by cohort members. This was lowest in the first year of the study (3,849 person-years) and highest in 2012 (185,227 person-years). Table 4.1 depicts patients at first OA diagnosis by the geographical region of their general practice.

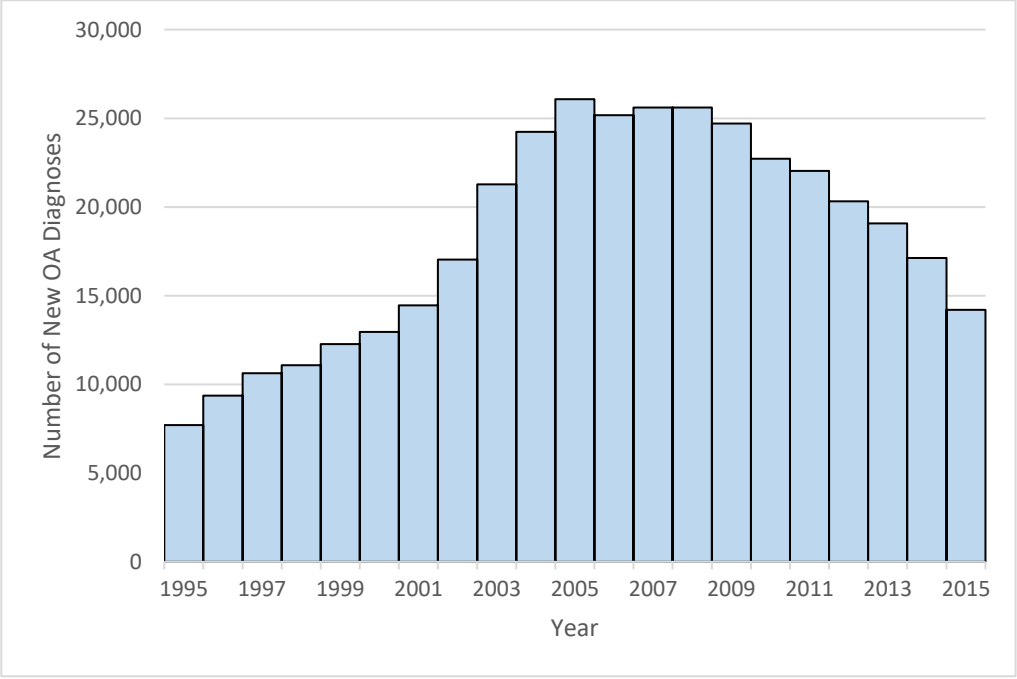


Figure 4.1 Number of Patients with a New Diagnosis of OA in the CPRD, by Year

Table 4.1 New OA Diagnoses by Geographical Region, 1995-2015

Region	Frequency	Percentage
North East	8,443	2.2
North West	50,390	13.1
Yorkshire & The Humber	17,710	4.6
East Midlands	17,535	4.6
West Midlands	41,205	10.7
East of England	34,664	9.0
South West	33,674	8.8
South Central	36,843	9.6
London	28,124	7.3
South East Coast	32,998	8.6
Northern Ireland	10,817	2.8
Scotland	31,547	8.2
Wales	39,730	10.4
Total	*383,680*	*100.0*

4.2 Outcome Events

Cohort members were followed for a median of 5.1 years (IQR: 2.3, 8.7; range: 0.0, 21.0) from the date of their index OA consultation to the occurrence of a censoring event. This provided a total of 2,270,238.8 person-years of follow-up. Censoring occurred when a cohort member reached the study end date (n = 122,518), transferred out of their practice (n = 62,973), died (n = 55,871) or received their first gabapentinoid prescription (n = 35,031). 117,874 cohort members were censored due to their general practice no longer uploading data to the CPRD.[21]

4.2.1 Cohort Members who Received a Gabapentinoid Prescription

35,031 (9.1%) patients received at least one prescription for a gabapentinoid. Of this subset of the population, 23,607 (67.4%) were female, and the median age at their first

[21] The number of censoring events (n = 394,267) adds to more than the number of members in the cohort (n = 383,680) due to the possibility of two or more censoring events occurring on the same day, such as a gabapentinoid prescription occurring on 31st December 2015, the study end date.

prescription was 69.0 years (IQR: 60.0, 77.0; range: 40, 106). As could be anticipated by the date of marketing authorisation of the gabapentinoids in the UK, there were less than 100 first gabapentinoid prescriptions annually during the period 1995-2000, and in the remainder of the study period the number of cohort members who received their first gabapentinoid prescription increased from 164 in 2001 to 4,629 in 2014.

Of the 35,031 first-time prescriptions prescribed across all years of the study period, 25,208 (72.0%) were formulations of gabapentin, with the remaining 9,823 (28.0%) prescriptions being pregabalin. Gabapentin was prescribed in each year of the study period, and the maximum number of first gabapentin prescriptions occurred in 2014 (n = 3,439). Pregabalin was first prescribed in this cohort in 2004, and the number of incident prescriptions peaked in 2010 (n = 1,197), where it accounted for 37.2% of gabapentinoids prescribed that year (Table 4.2). The ratio of gabapentin to pregabalin prescriptions was similar across age strata, lowest in the 40-49 years age group (where gabapentin accounted for 70.3% of first gabapentinoid prescriptions) and highest in the 70-79 years age group (72.6%).

Eight different formulations of gabapentin were the first gabapentinoid prescribed to patients with OA. The most common formulation was 300mg capsules. There were nine different formulations of first pregabalin prescriptions during the study period, of which 75mg capsules were the most common (Table 4.3).

Of the 35,031 patients who received a gabapentinoid, 3,904 (11.1%) underwent a total knee arthroplasty (TKA) during the study period (prior to all censoring events except first gabapentinoid prescription). Of this subgroup, 2,587 (66.3%) were female and median age at operation was 69.0 years (IQR: 62.3, 76.0; range: 43, 94).

Table 4.2 Number of First Gabapentin and Pregabalin Prescriptions Issued, by Year, to Patients with OA

Year	Gabapentin		Pregabalin		*Total*
	Number	Percentage	Number	Percentage	
1995	2	100.0	0	0.0	*2*
1996	4	100.0	0	0.0	*4*
1997	2	100.0	0	0.0	*2*
1998	8	100.0	0	0.0	*8*
1999	21	100.0	0	0.0	*21*
2000	87	100.0	0	0.0	*87*
2001	164	100.0	0	0.0	*164*
2002	321	100.0	0	0.0	*321*
2003	514	100.0	0	0.0	*514*
2004	690	96.1	28	3.9	*718*
2005	838	72.1	325	27.9	*1,163*
2006	910	64.2	507	35.8	*1,417*
2007	1,294	70.0	554	30.0	*1,848*
2008	1,584	68.7	721	31.3	*2,305*
2009	1,828	67.2	891	32.8	*2,719*
2010	2,017	62.8	1,197	37.2	*3,214*
2011	2,504	67.9	1,184	32.1	*3,688*
2012	2,814	72.4	1,075	27.6	*3,889*
2013	3,218	73.7	1,146	26.3	*4,364*
2014	3,439	74.3	1,190	25.7	*4,629*
2015	2,949	74.6	1,005	25.4	*3,954*
Total	*25,208*	*72.0*	*9,823*	*28.0*	*35,031*

Table 4.3 Formulations of the First Gabapentin or Pregabalin Prescribed to a Patient with OA, Ordered by Frequency[22]

Gabapentin		**Pregabalin**	
Formulation	Frequency	Formulation	Frequency
Gabapentin 300mg capsules	12,995	Pregabalin 75mg capsules	3,062
Gabapentin 100mg capsules	11,467	Pregabalin 25mg capsules	2,958
Gabapentin 600mg capsules	422	Pregabalin 50mg capsules	2,431
Gabapentin 400mg capsules	241	Pregabalin 150mg capsules	562
Gabapentin 800mg capsules	52	Pregabalin 100mg capsules	392
Gabapentin 50mg/ml solution	14	Pregabalin 300mg capsules	281
Gabapentin 250mg/5ml solution	10	Pregabalin 200mg capsules	103
Gabapentin 400mg/5ml solution	7	Pregabalin 225mg capsules	29
		Pregabalin 20mg/ml solution	5
Total	*25,208*	*Total*	*9,823*

[22] Different formulations of gabapentin and pregabalin have been grouped by dose, for instance 'Gabapentin 300mg capsules' includes 61 300mg Neurontin capsules and 2 gabapentin 300mg capsules produced by Teva UK Ltd. The full table is available in Appendix 3.1 on page 198.

4.3 Incidence of First Gabapentinoid Prescriptions in the OA Population

The crude annual incidence rate of first gabapentinoid prescriptions in patients diagnosed with OA increased through the study period (Table 4.4). In the period 1995-1999 the crude incidence rate of first gabapentinoid prescriptions in this cohort of patients with OA remained below 1.00 per 1,000 person-years. In the remaining period the incidence rate increased from 1.71 per 1,000 person-years (95% CI: 1.37, 2.11) in 2000 to 27.95 (95% CI: 27.15, 28.77) per 1,000 person-years in 2014. The incidence rate of first gabapentinoid prescriptions remained similar in 2015 (27.92 (95% CI: 27.06, 28.81) per 1,000 person years). The largest annual increase on the multiplicative scale occurred between 1999 and 2000 (crude incidence rate ratio: 3.29 (95% CI: 2.04, 5.30)), whilst the highest absolute rate difference occurred between years 2013 and 2014 (crude rate difference: 3.62 (95% CI: 2.54, 4.70) per 1,000 person-years).

Table 4.4 Events, Person-Time and Crude Incidence Rates, with 95% Confidence Intervals (CI)

Year	Events	Person-Years	Incidence Rate, per 1,000 person-years (95% CI)
1995	2	3,849.0	0.52 (0.06, 1.88)
1996	4	12,080.6	0.33 (0.09, 0.85)
1997	2	21,292.7	0.09 (0.01, 0.34)
1998	8	30,888.4	0.26 (0.11, 0.51)
1999	21	40,473.1	0.52 (0.32, 0.79)
2000	87	50,968.4	1.71 (1.37, 2.11)
2001	164	61,116.3	2.68 (2.29, 3.13)
2002	321	72,403.4	4.43 (3.96, 4.95)
2003	514	86,289.7	5.96 (5.45, 6.49)
2004	718	103,448.1	6.94 (6.44, 7.47)
2005	1,163	121,949.8	9.54 (9.00, 10.10)
2006	1,417	138,098.9	10.26 (9.73, 10.81)
2007	1,848	151,923.2	12.16 (11.62, 12.73)
2008	2,305	164,688.2	14.00 (13.43, 14.58)
2009	2,719	174,928.9	15.54 (14.96, 16.14)
2010	3,214	181,003.7	17.76 (17.15, 18.38)
2011	3,688	182,998.9	20.15 (19.51, 20.81)
2012	3,889	185,227.1	21.00 (20.34, 21.67)
2013	4,364	179,390.9	24.33 (23.61, 25.06)
2014	4,629	165,619.5	27.95 (27.15, 28.77)
2015	3,954	141,600.4	27.92 (27.06, 28.81)

The age-standardised incidence rate differed only marginally from the crude estimates and showed the same trend over time. The number of first gabapentinoid prescriptions remained below 1.00 per 1,000 person-years until the calendar year 2000, then increased annually to 27.57 (95% CI: 26.71, 28.43) in 2014. The incidence rate remained 27.57 (95% CI: 26.71, 28.43) first gabapentinoid prescriptions per 1,000 person-years in 2015 (Table 4.5).

Table 4.5 Crude Age-Stratified and Age-Standardised Rates of First Gabapentinoid Prescriptions, by Year

Year	Age Group										Age Standardised	
	40-49 Years		50-59 Years		60-69 Years		70-79 Years		80 Years and Over			
	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI
1995	0.00	(0.00, 10.83)	2.61	(0.32, 9.42)	0.00	(0.00, 3.46)	0.00	(0.00, 3.37)	0.00	(0.00, 6.33)	0.36	(0.00, 0.85)
1996	1.03	(0.03, 5.75)	0.42	(0.01, 2.33)	0.30	(0.01, 1.65)	0.30	(0.01, 1.66)	0.00	(0.00, 1.84)	0.26	(0.01, 0.51)
1997	0.67	(0.02, 3.71)	0.24	(0.01, 1.33)	0.00	(0.00, 0.62)	0.00	(0.00, 0.61)	0.00	(0.00, 1.02)	0.05	(0.00, 0.12)
1998	0.52	(0.01, 2.89)	0.50	(0.10, 1.45)	0.23	(0.03, 0.83)	0.11	(0.00, 0.62)	0.19	(0.00, 1.05)	0.23	(0.07, 0.39)
1999	0.43	(0.01, 2.41)	0.51	(0.14, 1.30)	0.71	(0.31, 1.40)	0.50	(0.18, 1.09)	0.28	(0.03, 1.02)	0.50	(0.29, 0.72)
2000	4.62	(2.46, 7.90)	1.72	(1.00, 2.76)	1.21	(0.70, 1.93)	1.70	(1.10, 2.50)	1.59	(0.89, 2.62)	1.61	(1.27, 1.95)
2001	4.02	(2.14, 6.88)	2.70	(1.85, 3.82)	2.63	(1.91, 3.53)	2.35	(1.68, 3.18)	2.88	(1.99, 4.02)	2.66	(2.25, 3.06)
2002	4.55	(2.65, 7.28)	4.60	(3.54, 5.87)	4.66	(3.76, 5.72)	4.65	(3.77, 5.68)	3.62	(2.70, 4.75)	4.38	(3.90, 4.86)
2003	7.55	(5.17, 10.67)	6.20	(5.06, 7.51)	5.66	(4.74, 6.70)	6.39	(5.43, 7.48)	5.12	(4.11, 6.31)	5.86	(5.35, 6.37)
2004	6.72	(4.63, 9.44)	6.87	(5.77, 8.13)	7.19	(6.24, 8.24)	7.28	(6.33, 8.33)	6.23	(5.20, 7.40)	6.92	(6.41, 7.42)
2005	10.38	(7.90, 13.39)	9.23	(8.03, 10.55)	9.80	(8.78, 10.90)	9.40	(8.40, 10.49)	9.46	(8.28, 10.75)	9.53	(8.98, 10.08)
2006	13.57	(10.84, 16.78)	10.62	(9.39, 11.97)	9.57	(8.63, 10.59)	10.79	(9.78, 11.88)	9.43	(8.32, 10.64)	10.14	(9.61, 10.67)
2007	13.44	(10.81, 16.53)	11.79	(10.53, 13.17)	12.35	(11.34, 13.42)	12.67	(11.63, 13.78)	11.24	(10.09, 12.49)	12.11	(11.56, 12.66)
2008	18.01	(15.01, 21.43)	15.11	(13.71, 16.62)	13.34	(12.33, 14.40)	14.86	(13.78, 16.01)	11.99	(10.85, 13.21)	13.80	(13.24, 14.37)
2009	20.05	(16.92, 23.59)	16.56	(15.11, 18.10)	15.38	(14.34, 16.48)	16.03	(14.94, 17.18)	13.39	(12.22, 14.63)	15.34	(14.77, 15.92)
2010	28.95	(25.18, 33.12)	19.89	(18.31, 21.56)	17.50	(16.41, 18.64)	17.45	(16.32, 18.63)	14.73	(13.54, 16.01)	17.40	(16.80, 18.00)
2011	30.26	(26.36, 34.58)	23.98	(22.24, 25.81)	19.10	(17.97, 20.28)	20.70	(19.47, 21.98)	16.22	(14.98, 17.53)	19.79	(19.15, 20.43)
2012	36.53	(32.16, 41.32)	26.42	(24.59, 28.35)	19.32	(18.19, 20.50)	20.90	(19.68, 22.18)	16.86	(15.61, 18.17)	20.57	(19.93, 21.22)
2013	40.28	(35.51, 45.51)	29.04	(27.07, 31.11)	22.16	(20.93, 23.45)	24.53	(23.20, 25.93)	21.11	(19.69, 22.59)	24.00	(23.29, 24.71)
2014	48.49	(42.89, 54.63)	35.11	(32.84, 37.49)	24.50	(23.14, 25.93)	28.51	(27.02, 30.05)	23.78	(22.23, 25.41)	27.57	(26.78, 28.37)
2015	44.06	(38.20, 50.55)	34.89	(32.46, 37.46)	26.90	(25.36, 28.51)	26.61	(25.05, 28.23)	23.85	(22.18, 25.61)	27.57	(26.71, 28.43)

N.B. All incidence rates are displayed per 1,000 person-years. (IR: annual incidence rate, CI: confidence interval)

As demonstrated by Table 4.5, and further displayed in Figure 4.2, the absolute increase in the incidence rate of first gabapentinoid prescriptions was seen in all age groups, but from the mid-2000s onwards patients aged 40-49 years at the time of prescription were most likely to receive their first gabapentinoid prescription. In contrast, those aged 80 years or older were least likely to receive their first prescription. The incidence rate in those aged 40-49 years increased from 4.62 (95% CI: 2.46, 7.90) first prescriptions per 1,000 person-years in 2000 to 44.06 (95% CI: 38.20, 50.55) in 2015. The incidence rate in those aged 80 years or older increased from 1.59 (95% CI: 0.89, 2.62) in 2000 to 23.85 (95% CI: 22.18, 25.61) in 2015. Between these two age strata (40-49 and 80 years and older), the absolute rate difference in 2000 and 2015 was 3.03 and 20.20 prescriptions per 1,000 person-years, respectively. However, during the same period the rate ratio of gabapentinoid prescribing in those aged 40-49 compared to those aged 80 years or older decreased from 2.91 in 2000 to 1.85 in 2015.

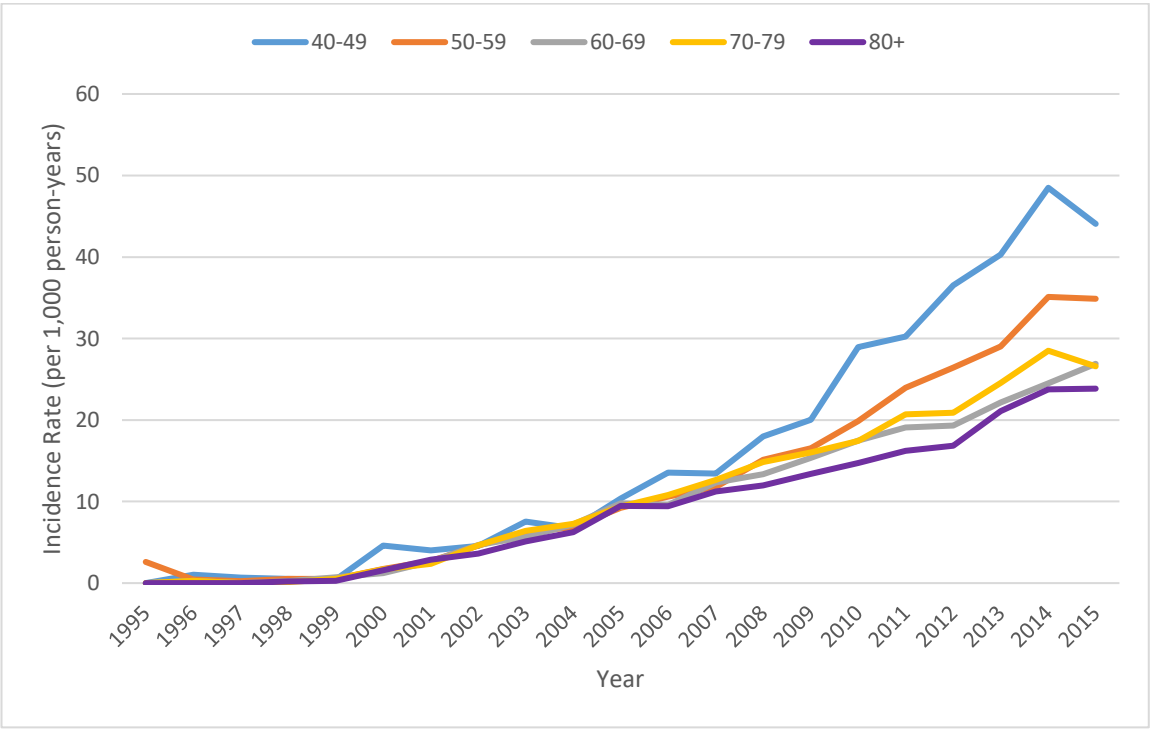


Figure 4.2 Crude Annual Incidence Rate of First Gabapentinoid Prescriptions, Stratified by Attained Age

Over the course of the study period, the crude incidence rate of first gabapentinoid prescriptions was 16.86 (95% CI: 16.65, 17.08) per 1,000 person-years in females, compared to 13.13 (95% CI: 12.89, 13.37) in males. This resulted in a female to male rate ratio over the study period of 1.28 (95% CI: 1.25, 1.31). This ratio remained fairly constant between 2000 and 2015 (1.24 (95% CI: 0.79, 1.94) in 2000, 1.33 (95% CI: 1.24, 1.42) in 2015). However, due to females being prescribed a gabapentinoid more frequently than males, the absolute rate difference increased from 0.35 more females per 1,000 person-years being first prescribed a gabapentinoid in 2000 to 7.77 in 2015. The crude incidence rates for females increased from 1.84 (95% CI: 1.40, 2.37) per 1,000 person years in 2000 to 31.02 (95% CI: 29.85, 32.22) in 2015. During the same period the crude incidence rate in males increased from 1.49 (95% CI: 0.99, 2.15) to 23.25 (95% CI: 22.01, 24.55). Age-standardisation of the gender-stratified data resulted in very similar incidence rates (Figure 4.3).

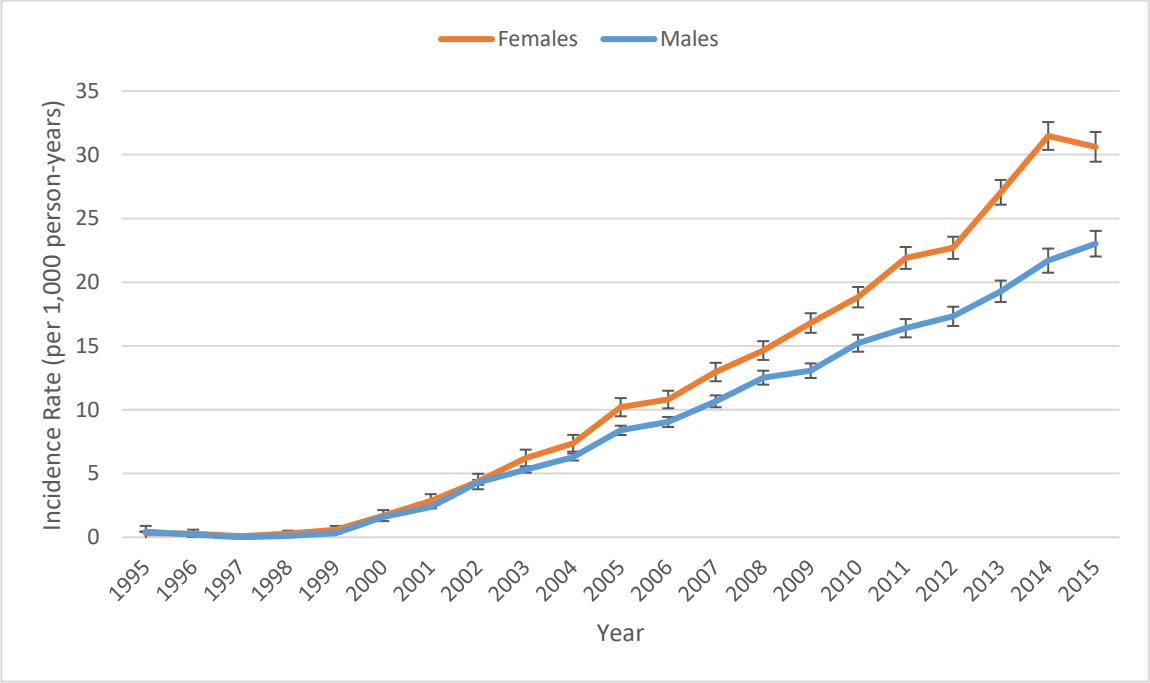


Figure 4.3 Age-Standardised Incidence Rate (with 95% Confidence Intervals) of First Gabapentinoid Prescriptions, Stratified by Gender

An increase in incidence rates across the study period was observed in all 13 geographical regions of the CPRD (Figure 4.4). Within the CPRD, there were at least 20 first gabapentinoid prescriptions issued to patients with OA (i.e. ≥20 patients with OA received their first gabapentinoid) annually from 2004 onwards.[23] Similar to the data stratified by age group and gender, the increase in incidence rates in the majority of regions slowed or decreased in 2015. Over the course of the study period, Northern Ireland, followed by Scotland, had the highest rates of first gabapentinoid prescriptions per 1,000 person-years (Figure 4.5). It should be noted that Northern Ireland, Scotland and Wales are individual regions in the CPRD, and as a result displayed prescribing rates are equal within each area. Northern Ireland had the highest incidence rates of patients with OA receiving their first gabapentinoid each year between 2005 and 2014, before being overtaken by the North East of England in 2015. The rate of first gabapentinoid prescriptions in the North East in 2015 was 44.46 (95% CI: 32.30, 59.69) per 1,000 person-years, the highest of any region during the study period. The second-highest rate of prescribing occurred in Northern Ireland in 2010 (44.18 (95% CI: 38.66, 50.26) per 1,000 person-years). During this year the next-highest rate of first gabapentinoid prescriptions was in Scotland (24.53 (95% CI: 21.97, 27.3) per 1,000 person-years), which was the largest absolute rate difference between the highest and second-highest rates of first prescriptions in a calendar year. During the period 2006 to 2012 South Central England consistently had the lowest rates of prescribing. The largest absolute change between years within a region occurred in the North East between years 2013 and 2014, an increase of 16.56 first prescriptions per 1,000 person-years.

[23] This was with the exception of the East Midlands, which had a severe drop off in the number of first gabapentinoid prescriptions as well as total person-time from 2014 onwards, due to many practices in this region leaving the CPRD at this time.

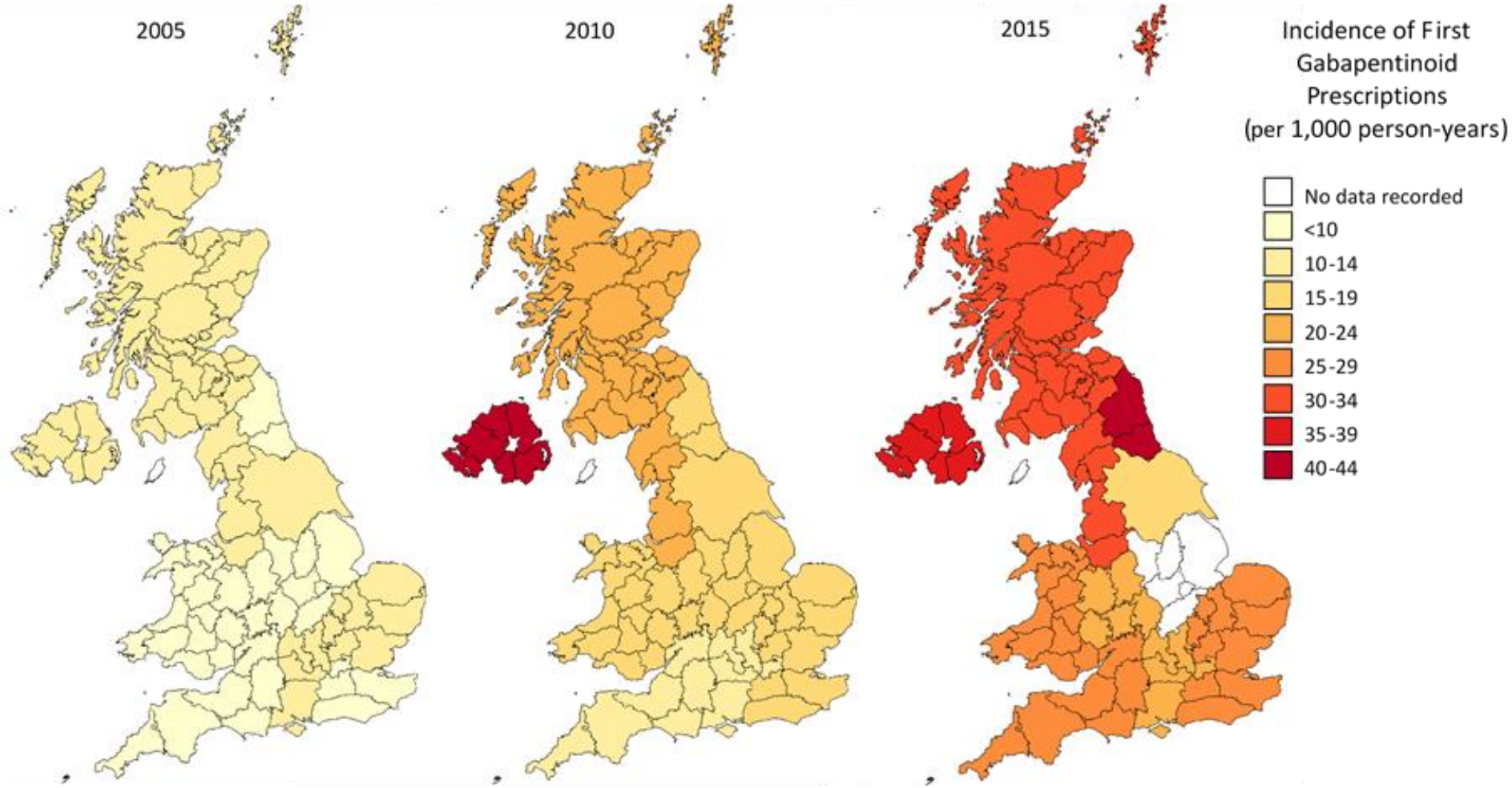


Figure 4.4 Crude Incidence (per 1,000 Person-Years) of First Gabapentinoid Prescriptions in a Cohort of Patients with OA in 2005, 2010 and 2015.

Maps created on www.mapchart.net. N.B East Midlands (in white) in 2015 had no data contributed to the CPRD, due to all cohort members being censored prior to this year.

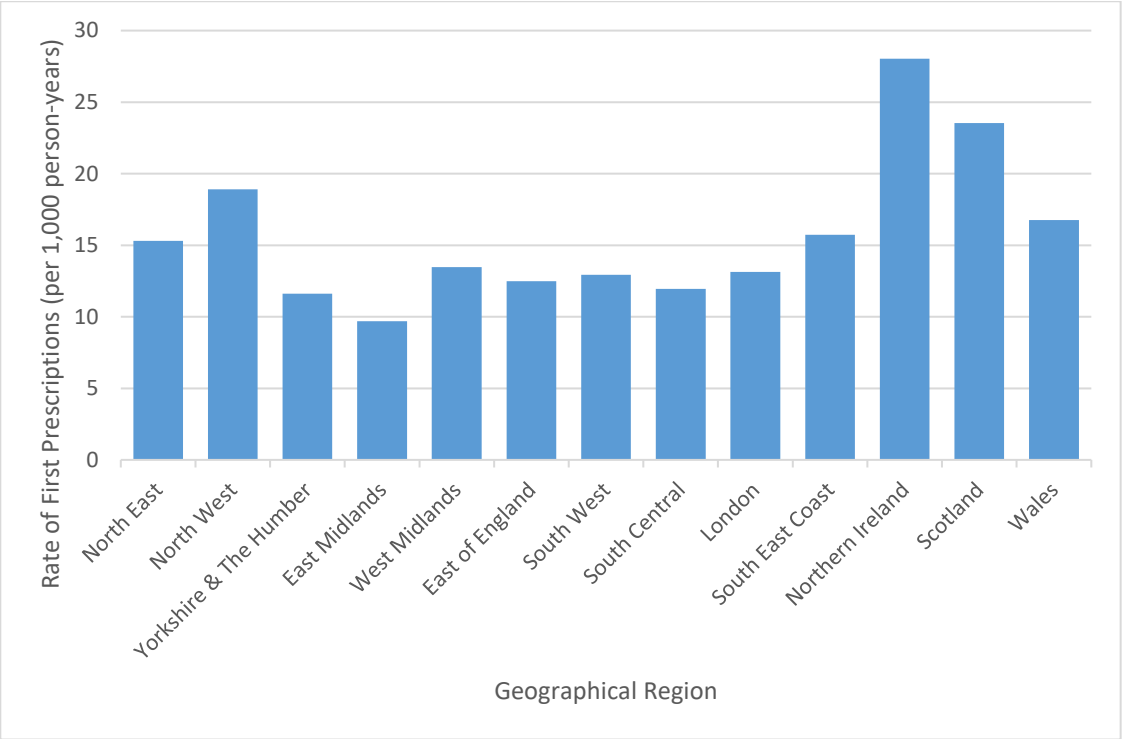


Figure 4.5 Crude Incidence Rate of First Gabapentinoid Prescriptions, Between 1995 and 2015, by Geographical Region

Crude incidence rates increased in all strata of time since diagnosis through the study period, but this was most pronounced in those prescribed their first gabapentinoid within five years of their OA diagnosis (Figure 4.6). Of the 22,093 first gabapentinoid prescriptions that occurred within 5 years of a patient's index OA consultation, 5,841 (26.4%) occurred within 90 days of the OA diagnosis being given. This finding, perhaps unexpected from clinical experience, will be discussed further in Chapter 6. The pattern of higher incidence rates in the shortest duration was seen across all age strata.

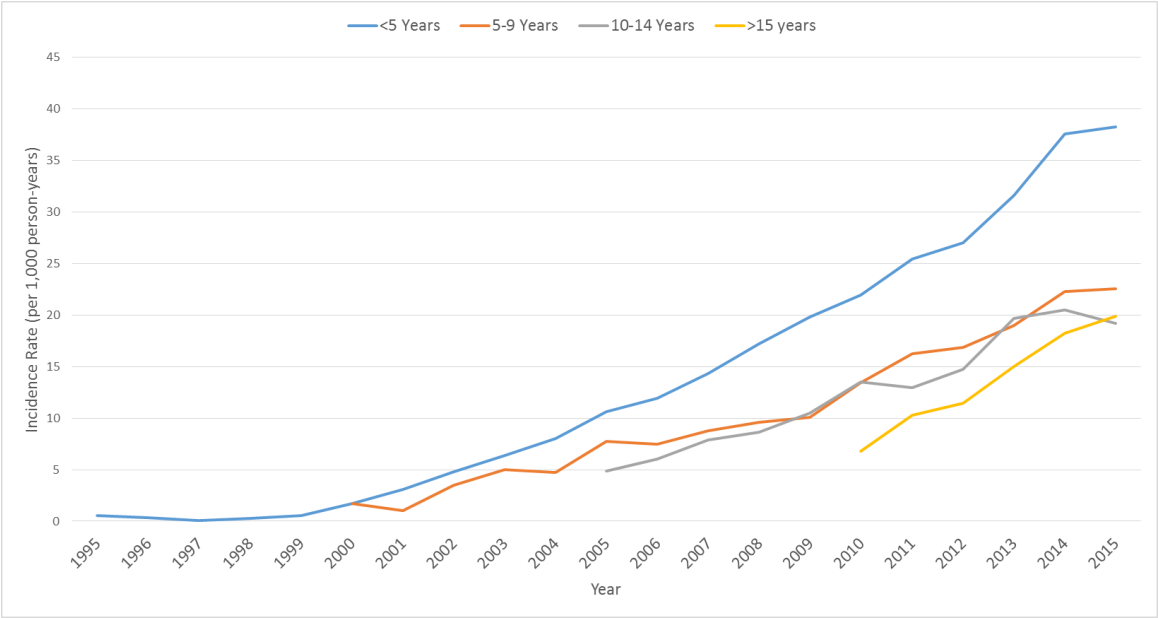


Figure 4.6 Crude Incidence Rates of First Gabapentinoid Prescriptions, by Time Since Index OA Consultation

4.4 Summary

There has been an increase in the rate of first gabapentinoid prescriptions to patients diagnosed with OA. Incidence rates were highest in younger age groups, females, as well as the North of England, Northern Ireland and Scotland. Incidence rates were not higher in those with longer time since index OA consultation, but were instead highest within five years of diagnosis. The next chapter will further analyse the 35,031 patients with OA prescribed a gabapentinoid, by attributing these prescriptions to OA as well as to licensed and unlicensed indications.

5 Results II

5.1 Primary Analysis

The primary attribution analysis explored the proportion of first gabapentinoid prescriptions prescribed to the study cohort that were attributable to OA, as well as to licensed and unlicensed indications, during the first specified time window (14 days before a cohort member's gabapentinoid prescription to 90 days after).

5.1.1 Attribution of First Gabapentinoid Prescriptions to Osteoarthritis

Within window 1, 3,628 (10.4%; 95% CI: 10.0, 10.7) of the 35,031 cohort members prescribed a gabapentinoid had a diagnostic OA Read code recorded. 2,274 (62.7%) of these OA consultations were the patient's index OA consultation. 1,082 (3.1%) of all patients prescribed a gabapentinoid had a Read code for OA recorded on the same day as the prescription was issued.

Within the first time window studied, the proportion of first gabapentinoid prescriptions attributed to OA was similar by gender. 10.6% of first prescriptions in males were attributed to the condition, compared to 10.3% in females. The proportion of first prescriptions attributed to OA was also similar in each region of the CPRD. The proportion of first prescriptions attributed to OA was inversely associated with a patient's age at prescription (Table 5.1). Across all years of the study, a first prescription of pregabalin (11.9%) was more likely to be attributed to OA than first gabapentin prescriptions (9.8%). This slight increase in pregabalin attribution remained even when data from only 2004 onwards, the year of

pregabalin approval, was analysed. First prescriptions could be attributed to OA in all years of the study period, except 1996, and from 2001 onwards (when there were more than 100 first prescriptions annually to patients with OA in the CPRD), the proportion of first prescriptions attributed to OA was similar across all calendar years of the study (Table 5.2).

Table 5.1 Attribution of First Gabapentinoid Prescriptions to OA, by Age Group

Window 1: 14 days before gabapentinoid prescription to 90 days after		
Age Group	Number of Prescriptions	Attributed to OA (%)
40-49	2,031	347 (17.1)
50-59	6,603	836 (12.7)
60-69	9,895	1,076 (10.9)
70-79	10,111	864 (8.6)
80+	6,391	505 (7.9)
Total	*35,031*	*3,628 (10.4)*

Table 5.2 Attribution of First Gabapentinoid Prescriptions to OA, by Calendar Year

Window 1: 14 days before gabapentinoid prescription to 90 days after		
Year	Number of Prescriptions	Attributed to OA (%)
1995	2	1 (50.0)
1996	4	0 (-)
1997	2	1 (50.0)
1998	8	1 (12.5)
1999	21	4 (19.1)
2000	87	6 (6.9)
2001	164	17 (10.4)
2002	321	37 (11.5)
2003	514	65 (12.7)
2004	718	100 (13.9)
2005	1163	129 (11.1)
2006	1417	167 (11.8)
2007	1848	219 (11.9)
2008	2305	223 (9.7)
2009	2719	286 (10.5)
2010	3214	300 (9.3)
2011	3688	354 (9.6)
2012	3889	403 (10.4)
2013	4364	398 (9.1)
2014	4629	506 (10.9)
2015	3954	411 (10.4)

5.1.2 Attribution of First Gabapentinoid Prescriptions to Licensed or Unlicensed Indications

During the first time window, 4,706 (13.4%; 95% CI: 13.1, 13.8) of the 35,031 cohort members prescribed a gabapentinoid had at least one Read code for a licensed or unlicensed indication. As patients could have a Read code for more than one condition during the same time window, there were 4,774 Read codes in this subgroup of the population.[24] 4,176 (87.5%) of these Read codes were of licensed indications.[25] 13 cohort members had two licensed indications present within the first window of their first gabapentinoid prescription. 594 (1.7%) patients had a Read code of an unlicensed indication, of which 51 also had a licensed indication recorded within window 1 (Table 5.3).[26]

Table 5.3 Attribution of First Gabapentinoid Prescriptions to Licensed or Unlicensed Indications

Window 1: 14 days before gabapentinoid to 90 days after		
Indication Type	Number	%
Only Licensed Indication(s) Present	4,112	11.7
Only Unlicensed Indication(s) Present	543	1.6
Licensed and Unlicensed Indication (s) Present	51	0.2
Total	*4,706*	*13.4*

Of the licensed indications, neuropathic pain was the most common condition for a first prescription to be attributed to, followed by epilepsy and generalised anxiety disorder (GAD). Of the 4,058 neuropathic pain Read codes, over 50% were accounted for by sciatica

[24] Whilst cohort members could only have one code of each condition, as the consultation date closest to prescription was taken, patients could have more than one licensed or unlicensed indication, for instance if they had Read codes for both epilepsy and neuropathic pain. Cohort members could also have both a licensed and unlicensed indication, and therefore the total number of Read codes exceeds the number of cohort members to which they were given.

[25] Licensed indications: Epilepsy, Generalised Anxiety Disorder, Neuropathic Pain.

[26] Unlicensed indications: Attention Deficit Disorder, Alcohol Withdrawal, Bipolar Disorder, Complex Regional Pain Syndrome, Fibromyalgia, Menopausal Hot Flushes, Migraine, Panic Disorder, Restless Legs Syndrome.

(1,291 (31.8%)), a non-specific neuropathic pain Read code (478 (11.8%)), and shingles (464 (11.4%)).

Of the unlicensed indications, fibromyalgia was the most commonly occurring Read code within window 1 of a cohort member's first gabapentinoid prescription (Table 5.4). Fewer than 10 prescriptions were attributed to attention deficit disorder, alcohol withdrawal and bipolar disorder. For the remaining indications, the most common date for this condition to appear in a cohort member's healthcare records was on the same date as their gabapentinoid prescription.

Table 5.4 Attribution of First Gabapentinoid Prescriptions to Licensed and Unlicensed Indications, by Condition

Window 1: 14 days before gabapentinoid to 90 days after		
Condition	Number	% (95% CI)
Epilepsy	71	0.2 (0.2, 0.3)
GAD	47	0.1 (0.1, 0.2)
Neuropathic Pain	4,058	11.6 (11.3, 11.9)
Attention Deficit Disorder	0	-
Alcohol Withdrawal	2	<0.1 (-)
Bipolar Disorder	9	<0.1 (-)
CRPS	37	0.1 (0.1, 0.1)
Fibromyalgia	196	0.6 (0.5, 0.6)
Menopausal Hot Flushes	67	0.2 (0.2, 0.2)
Migraine	85	0.2 (0.2, 0.3)
Panic Disorder	41	0.1 (0.1, 0.2)
Restless Legs Syndrome	161	0.5 (0.4, 0.5)
Total Read Codes	*4,774*	-
Total Cohort Members	*4,706*	*13.4 (13.1, 13.8)*

Stratification of prescriptions by calendar year demonstrated that the first gabapentinoid prescription to patients with OA attributed to a licensed indication occurred in 1999 (neuropathic pain), and a year later for unlicensed indications (restless legs syndrome).

Between 2005 and 2015 the proportion of patients receiving a gabapentinoid that could be attributed to a licensed or unlicensed indication remained fairly constant (between 12.0% and 14.8%).

The proportion of first gabapentinoid prescriptions attributable to licensed or unlicensed indications (combined) was similar in males (1,493 (13.1%)) and females (3,213 (13.6%)) (Table 5.5). Females were more likely than males to have their first gabapentinoid prescription attributed to an unlicensed indication.

Table 5.5 Attribution of First Prescriptions to Licensed or Unlicensed Indications, by Gender

Window 1	Male		Female	
	Prescriptions	11,424	Prescriptions	23,607
Condition	Number	% (95% CI)	Number	% (95% CI)
Epilepsy	22	0.2 (0.1, 0.3)	49	0.2 (0.2, 0.3)
GAD	13	0.2 (0.1, 0.2)	34	0.1 (0.1, 0.2)
Neuropathic Pain	1,359	11.9 (11.3, 12.5)	2,699	11.4 (11.0, 11.8)
Attention Deficit Disorder	0	-	0	-
Alcohol Withdrawal	1	<0.1 (-)	1	<0.1 (-)
Bipolar Disorder	2	<0.1 (-)	7	<0.1 (-)
CRPS	14	0.1 (0.1, 0.2)	23	0.1 (0.1, 0.1)
Fibromyalgia	21	0.2 (0.1, 0.3)	175	0.7 (0.6, 0.9)
Menopausal Hot Flushes	0	<0.1 (-)	67	0.3 (0.2, 0.4)
Migraine	15	0.1 (0.1, 0.2)	70	0.3 (0.2, 0.4)
Panic Disorder	10	0.1 (0.0, 0.1)	31	0.1 (0.1, 0.2)
Restless Legs Syndrome	48	0.4 (0.3, 0.5)	113	0.5 (0.4, 0.6)
Total Read Codes	*1,505*	-	*3,269*	-
Total Cohort Members	*1,493*	*13.1 (12.5, 13.7)*	*3,213*	*13.6 (13.2, 14.1)*

(GAD: generalised anxiety disorder, CRPS: complex regional pain syndrome). Proportions are displayed as percentages with 95% confidence intervals (CIs)

Unlike in the attribution of first prescriptions to OA, the proportion of first prescriptions attributed to a licensed indication increased proportionally with patient's age at prescription. 226 indication Read codes featured in the electronic health records of 219 patients aged 40-49 years during window 1. This 10.8% of patients with a first prescription attributable to a licensed or unlicensed indication increased to 14.8% in those aged 80 years or older (Table 5.6). Through each of the age groups, the proportion of patients with a neuropathic pain Read code increased. 66.7% of prescriptions attributed to licensed or unlicensed indications in those aged 40-49 years were due to neuropathic pain, compared to 93.5% of prescriptions in those aged 80 years or older. Patients who had a gabapentinoid prescription that could be attributed to epilepsy or GAD were most commonly in the age group 60-69 years. The proportion of first prescriptions attributed to unlicensed conditions was highest in those aged 40-49 years at prescriptions, and lowest in those aged 80 years or older.

There was a 1.4-fold variation in attribution of gabapentinoid prescriptions when stratified by the 13 geographical regions of the CPRD (Table 5.7). The lowest proportion of prescriptions attributed to a licensed or unlicensed indication occurred in Yorkshire and The Humber (11.4%) and the highest occurred in the East of England (16.1%). Perhaps due to the majority of attribution being to neuropathic pain, the regional variation specific to this condition was very similar. Within GAD and epilepsy, the other licensed indications, the highest proportion of attributed prescriptions occurred in the East Midlands. The highest and lowest proportions of prescriptions attributed to unlicensed indications occurred in the South West of England and London, respectively.

Table 5.6 Attribution of First Gabapentinoid Prescriptions to a Licensed or Unlicensed Indication, by Attained Age

Window 1	40-49		50-59		60-69		70-79		80+	
	Prescriptions 2,031		Prescriptions 6,603		Prescriptions 9,895		Prescriptions 10,111		Prescriptions 6,391	
Condition	Number	%	Number	%	Number	%	Number	%	Number	%
Epilepsy	3	0.2	13	0.2	27	0.3	15	0.2	13	0.2
GAD	1	0.1	9	0.1	17	0.2	12	0.1	8	0.1
Neuropathic Pain	146	7.2	562	8.5	1,131	11.4	1,333	13.2	886	13.9
Attention Deficit Disorder	0	-	0	-	0	-	0	-	0	-
Alcohol Withdrawal	1	0.1	1	<0.1	0	-	0	-	0	-
Bipolar Disorder	1	0.1	1	<0.1	2	<0.1	3	<0.1	2	<0.1
CRPS	2	0.1	17	0.3	8	0.1	8	0.1	2	<0.1
Fibromyalgia	36	1.8	83	1.3	56	0.6	18	0.2	3	0.1
Menopausal Hot Flushes	11	0.5	24	0.4	22	0.2	9	0.1	1	<0.1
Migraine	12	0.6	25	0.4	27	0.3	13	0.1	8	0.1
Panic Disorder	4	0.2	10	0.2	7	0.1	13	0.1	7	0.1
Restless Legs Syndrome	9	0.4	19	0.3	47	0.5	54	0.5	32	0.5
Total Read Codes	*226*	-	*764*	-	*1,344*	-	*1,478*	-	*962*	-
Total Cohort Members	*219*	*10.8*	*747*	*11.3*	*1,329*	*13.4*	*1,463*	*14.4*	*948*	*14.8*
(95% CI)	*(9.4, 12.1)*		*(10.6, 12.1)*		*(12.8, 14.1)*		*(13.8, 15.2)*		*(14.0, 15.7)*	

(GAD: generalised anxiety disorder, CRPS: complex regional pain syndrome)

Table 5.7 Attribution of First Gabapentinoid Prescriptions to Licensed or Unlicensed Indications, by Geographical Region

Window 1 Region	Prescriptions in Cohort	Licensed Number (%)	Unlicensed Number (%)	Licensed or Unlicensed[27] Number (%)
North East	801	99 (12.4)	12 (1.5)	111 (13.9)
North West	5,979	789 (13.2)	107 (1.8)	886 (14.8)
Yorkshire & The Humber	1,140	113 (9.9)	21 (1.8)	130 (11.4)
East Midlands	958	121 (12.6)	16 (1.7)	137 (14.3)
West Midlands	3,396	420 (12.4)	73 (2.2)	486 (14.3)
East of England	2,518	374 (14.9)	35 (1.4)	406 (16.1)
South West	2,547	280 (11.0)	59 (2.3)	333 (13.1)
South Central	2,604	328 (12.6)	41 (1.6)	364 (14.0)
London	2,179	240 (11.0)	30 (1.4)	268 (12.3)
South East Coast	2,933	325 (11.1)	55 (1.9)	376 (12.8)
Northern Ireland	1,889	218 (11.5)	31 (1.6)	249 (13.2)
Scotland	3,855	404 (10.5)	54 (1.4)	453 (11.8)
Wales	4,232	452 (10.7)	60 (1.4)	507 (12.0)

Stratification by gabapentinoid type demonstrated that, whilst some indications were present in the first time window surrounding both gabapentin and pregabalin equally, there were some differences in certain conditions. For instance GAD, which is a licensed indication for pregabalin but not of gabapentin, appeared more frequently around the time of a cohort member's first pregabalin prescription compared to those prescribed gabapentin. Attributed prescriptions of gabapentin were more likely to be due to Read codes of neuropathic pain, menopausal hot flushes and restless legs syndrome. In total, gabapentin prescriptions were more likely to be attributed to a licensed or unlicensed indication than pregabalin (Table 5.8).

[27] Patients with licensed and unlicensed indications may have been mutually exclusive (such as in the North East), but could have had Read codes of both licensed and unlicensed indications, resulting in the attribution of first prescriptions to licensed or unlicensed conditions not totalling the individual attribution, such as in the North West.

Table 5.8 Attribution of First Gabapentin or Pregabalin Prescriptions to Licensed or Unlicensed Indications

Window 1	Gabapentin Prescriptions: 25,208		Pregabalin Prescriptions: 9,823	
Condition	Number	%	Number	%
Epilepsy	55	0.2	16	0.2
GAD	8	<0.1	39	0.4
Neuropathic Pain	3,117	12.4	941	9.6
Attention Deficit Disorder	0	-	0	-
Alcohol Withdrawal	1	<0.1	1	<0.1
Bipolar Disorder	6	<0.1	3	<0.1
CRPS	22	0.1	15	0.2
Fibromyalgia	132	0.5	64	0.7
Menopausal Hot Flushes	57	0.2	10	0.1
Migraine	70	0.3	15	0.2
Panic Disorder	29	0.1	12	0.1
Restless Legs Syndrome	140	0.6	21	0.2
Total (95% CI)	*3,637*	*14.4 (14.0, 14.9)*	*1,137*	*11.6 (10.9, 12.2)*

5.1.3 Attribution of First Gabapentinoid Prescriptions Solely to OA

As patients may have had Read codes of both OA and a licensed or unlicensed indication in the first time window studied, the 10.4% of first gabapentinoids attributed to OA may be the upper limit of prescriptions attributable to OA based on the presence of a Read code for the condition. 3,303 (9.4%; 95% CI: 9.1, 9.7) of all patients prescribed a gabapentinoid had an OA Read code within the first time window, with no licensed or unlicensed indication code recorded. Of these OA Read codes, 2,111 (63.9%) were their initial OA diagnosis. When stratified by patient age, gender and region, the proportion of attribution to patients solely with OA were similar to those attributed to OA with or without a licensed or unlicensed indication.

5.1.4 Unattributed Prescriptions

8,009 patients had a Read code within the first time window of OA or at least one of the identified licensed or unlicensed indications. As a result, 27,022 (77.1%; 95% CI: 76.7, 77.6) first gabapentinoid prescriptions issued to patients with OA were unattributed to OA or the other identified indications.

As seen in the attribution of first gabapentinoid prescriptions to OA and the licensed or unlicensed indications, the proportion of unattributed first prescriptions was similar between patient gender and region, as well as by calendar year and gabapentinoid type. Those aged 40-49 years at prescription had the lowest proportion of unattributed prescriptions, but the proportion in all other age groups was similar.

5.2 Sensitivity Analyses

As one may expect, expansion of the time window studied around the date of prescription resulted in an increased number of first gabapentinoid prescriptions being attributed to OA and licensed or unlicensed indications, resulting in a subsequent decrease in the proportion of unattributed prescriptions. The percentage of patients with a gabapentinoid prescription attributed to OA increased from 10.4% in window 1 to 28.4% in window 2 (180 days either side of prescription). In window 3 (365 days before gabapentinoid to 180 days after) the percentage of cohort members with an OA Read code was 37.1% (Table 5.9). As window 4 (365 days before OA diagnosis to 180 days after gabapentinoid prescription) spanned a patient's index date, this was not included in the analysis of OA attribution (as all patients' index dates would appear in this time window, and thus attribution would be 100%).

Table 5.9 Attribution of First Gabapentinoid Prescriptions to OA, by Time Window

Window	Definition	Number	% (95% CI)
1	-14d→G→+90	3,628	10.4 (10.0, 10.7)
2	-180d→G→+180	9,959	28.4 (28.0, 28.9)
3	-365d→G→+180	12,986	37.1 (36.6, 37.6)

N. B. G: Gabapentinoid, d: days (i.e. -14d→G = 14 days before gabapentinoid prescription date). This does not exclude patients who also have a licensed or unlicensed indication

As in the first time window studied, during the other time windows analysed the attribution of first gabapentinoid prescriptions to OA was similar between males and females. The proportion of first prescriptions attributed to OA was also similar between regions, although Scotland had the highest rates of attribution in windows 2 and 3. Pregabalin was more commonly attributed to OA than gabapentin in all time windows analysed, and attribution to OA was again inversely proportional to a patient's attained age. During window 3, the attribution of first gabapentinoid prescriptions to OA gradually decreased over the course of the study period (Figure 5.1).

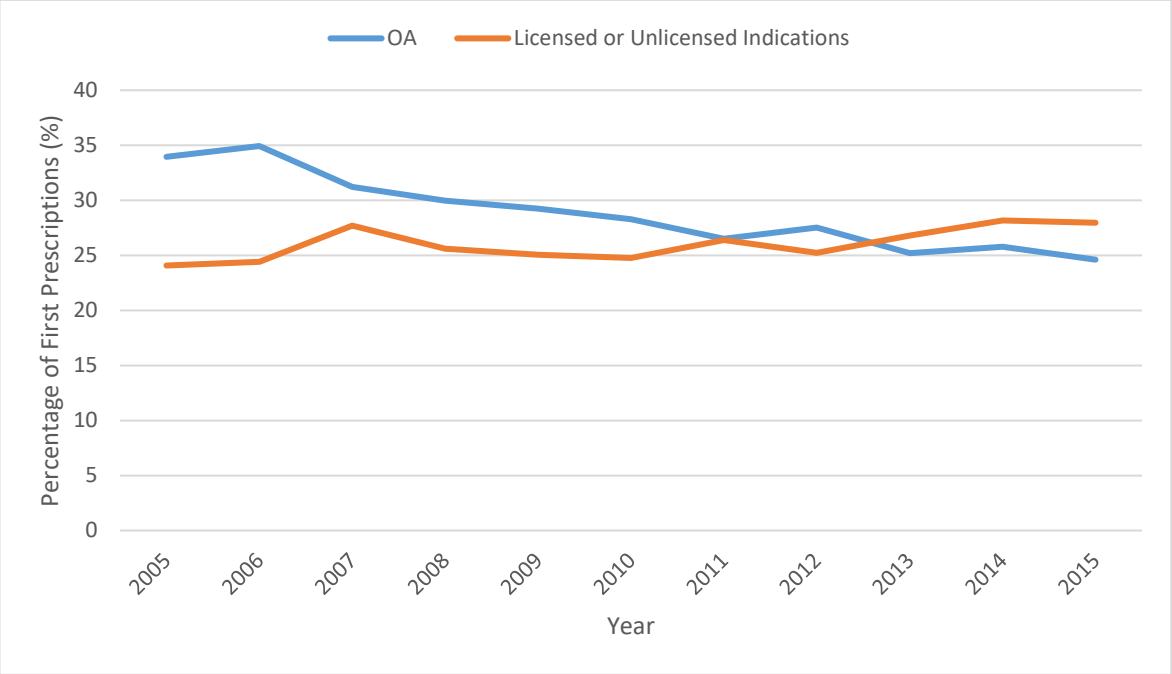


Figure 5.1 Attribution of First Gabapentinoid Prescriptions in Window 3 to OA (With No Presence of Licensed or Unlicensed Indications) and Licensed or Unlicensed Indications

The percentage of cohort members with a licensed or unlicensed indication increased from 13.4% in window 1 to 22.3% in window 2, 26.1% in window 3 and 41.0% in window 4. The proportion of first gabapentinoid prescriptions in patients with OA attributed to licensed or unlicensed indications, whilst similar in window 1, was higher in women throughout all windows studied. This difference increased as the time window surrounding a cohort member's first gabapentinoid prescription was expanded (Table 5.10). First prescriptions were also more likely to be attributed to an unlicensed indication in females in all time periods analysed. Differences between the original time window and the expanded time periods occurred in the analysis of the licensed indications. In windows 1 to 3, males who received a gabapentinoid were more likely to have a Read code for a licensed indication. However, in window 4 females had a higher proportion of attributed prescriptions, likely due to the same pattern seen with neuropathic pain. Epilepsy Read codes were more likely to be seen in the healthcare records of female patients in window 1, although males had a higher proportion of attribution in the remaining time windows studied.

Table 5.10 Attribution of First Gabapentinoid Prescriptions to Licensed or Unlicensed Indications, by Gender and Time Window

Window	Definition	Males	Females	*Total*
		Number (%)	Number (%)	*Number (%; 95% CI)*
1	-14d→G→+90d	1,493 (13.1)	3,213 (13.6)	*4,706 (13.4; 13.1, 13.8)*
2	-180d→G→+180d	2,468 (21.6)	5,331 (22.6)	*7,799 (22.3; 21.8, 22.7)*
3	-365d→G→+180d	2,825 (24.7)	6,302 (26.7)	*9,127 (26.1; 25.6, 26.5)*
4	-365d→OA, G→+180d	4,162 (36.4)	10,197 (43.2)	*14,359 (41.0; 40.5, 41.5)*

N.B. d: days, G: gabapentinoid, OA: osteoarthritis

As in window 1, the majority of licensed or unlicensed indication Read codes identified in all time windows studied were codes of neuropathic pain, although the proportion of codes that were neuropathic pain progressively decreased in each window (85.0% of all licensed

or unlicensed indication Read codes in window 1, 66.84% of Read codes in window 4). With the exception of attention deficit disorder, which first appeared in window 3, the attribution of prescriptions to all other conditions increased with each expansion of the window studied. Fibromyalgia remained the most common indication of the unlicensed conditions in windows 2 and 3, before being overtaken by migraine and menopausal hot flushes in the final time window (Table 5.11).

Table 5.11 Attribution of First Gabapentinoid Prescriptions to Licensed and Unlicensed Conditions, by Time Window

Condition	Window 1	Window 2	Window 3	Window 4
	-14d→G→+90d	-180d→G→+180d	-365d→G→+180d	-365d→OA, G→+180d
	Number (%)	Number (%)	Number (%)	Number (%)
Epilepsy	71 (0.2)	179 (0.5)	211 (0.6)	291 (0.8)
GAD	47 (0.1)	78 (0.2)	92 (0.3)	189 (0.5)
Neuropathic Pain	4,058 (11.6)	6465 (18.5)	7,404 (21.1)	11,164 (31.9)
Attention Deficit Disorder	0 (-)	0 (-)	2 (<0.1)	7 (<0.1)
Alcohol Withdrawal	2 (<0.1)	8 (<0.1)	11 (<0.1)	33 (0.1)
Bipolar Disorder	9 (<0.1)	23 (0.1)	31 (0.1)	101 (0.3)
CRPS	37 (0.1)	71 (0.2)	83 (0.2)	114 (0.3)
Fibromyalgia	196 (0.6)	355 (1.0)	443 (1.3)	820 (2.3)
Menopausal Hot Flushes	67 (0.2)	186 (0.5)	293 (0.8)	1,169 (3.3)
Migraine	85 (0.2)	251 (0.7)	365 (1.0)	1,183 (3.4)
Panic Disorder	41 (0.1)	129 (0.4)	206 (0.6)	692 (2.0)
Restless Legs Syndrome	161 (0.5)	318 (0.9)	441 (1.3)	939 (2.7)
Total Read Codes	*4,774*	*8,063*	*9,582*	*16,702*
Total Cohort Members	*4,706 (13.4)*	*7,799 (22.3)*	*9,127 (26.1)*	*14,359 (41.0)*

N.B. Percentages use the total number of gabapentinoid prescriptions (n = 35,031) as the denominator. (d: days, G: gabapentinoid, OA: osteoarthritis, GAD: generalised anxiety disorder, CRPS: complex regional pain syndrome)

In all time windows studied, the proportion of first gabapentinoid prescriptions attributable to licensed or unlicensed indications was higher in gabapentin than pregabalin. Stratification by region demonstrated that, similar to the initial analysis, the East of England

had the highest proportion of prescriptions attributed to licensed conditions in all time periods analysed. However, after the first time window, the area with the lowest proportion of attributed prescriptions was Scotland. During windows 1 to 3, the attribution of first gabapentinoid prescriptions to licensed or unlicensed indications remained fairly constant between 2005 and 2015. Analysis of window 4 demonstrated that the attribution of first gabapentinoids has increased during this period (Table 5.12).

Table 5.12 Attribution of First Gabapentinoid Prescriptions to Licensed or Unlicensed Indication, by Year

Year	Prescriptions	Window 1	Window 2	Window 3	Window 4
		-14d→G→+90d	-180d→G→+180d	-365d→G→+180d	-365d→OA, G→+180d
		Number (%)	Number (%)	Number (%)	Number (%)
1995	2	0 (-)	0 (-)	1 (50.0)	1 (50.0)
1996	4	0 (-)	0 (-)	0 (-)	1 (25.0)
1997	2	0 (-)	0 (-)	0 (-)	0 (-)
1998	8	0 (-)	1 (12.5)	1 (12.5)	1 (12.5)
1999	21	2 (9.5)	5 (23.8)	5 (23.8)	8 (38.1)
2000	87	10 (11.5)	17 (19.5)	23 (26.4)	32 (36.8)
2001	164	10 (6.1)	23 (14.0)	34 (20.7)	46 (28.1)
2002	321	40 (12.5)	57 (17.8)	63 (19.6)	98 (30.5)
2003	514	36 (7.0)	82 (16.0)	99 (19.3)	152 (29.6)
2004	718	70 (9.8)	138 (19.2)	163 (22.7)	218 (30.4)
2005	1,163	147 (12.6)	243 (20.9)	280 (24.1)	415 (35.7)
2006	1,417	175 (12.4)	292 (20.6)	346 (24.4)	505 (35.6)
2007	1,848	271 (14.7)	433 (23.4)	512 (27.7)	709 (38.4)
2008	2,305	283 (12.3)	501 (21.7)	590 (25.6)	840 (36.4)
2009	2,719	360 (13.2)	585 (21.5)	681 (25.1)	1,043 (38.4)
2010	3,214	415 (12.9)	684 (21.3)	796 (24.8)	1,268 (39.5)
2011	3,688	534 (14.5)	826 (22.4)	973 (26.4)	1,530 (41.5)
2012	3,889	467 (12.0)	830 (21.3)	981 (25.2)	1,597 (41.1)
2013	4,364	622 (14.3)	1,011 (23.2)	1,169 (26.8)	1,940 (44.5)
2014	4,629	686 (14.8)	1,138 (24.6)	1,304 (28.2)	2,102 (45.4)
2015	3,954	578 (14.6)	933 (23.6)	1,106 (28.0)	1,853 (46.9)

d: days, G: gabapentinoid, OA: osteoarthritis

In all time windows studied, the highest proportion of attribution to licensed or unlicensed indications occurred in those aged 80 years or older. First prescriptions were least likely to be attributed in cohort members aged 40-49 years in windows 1 and 4, with attribution of prescriptions in those aged 50-59 years lowest in the other time windows studied.

Similar results of the proportion of prescriptions attributed to other indications when stratified by gabapentinoid type remained upon expansion of the time period studied around the date of prescription. In all time windows studied the proportion of first pregabalin prescriptions attributed to GAD was higher than gabapentin. Within window 4 the proportion of pregabalin attributed to bipolar disorder and fibromyalgia was also larger than gabapentin prescriptions. Similar to the initial analysis, first gabapentin prescriptions were attributed to neuropathic pain and restless legs syndrome at a higher rate than those of pregabalin. In all windows studied, the proportion of gabapentin prescriptions attributed to licensed or unlicensed indications was higher than that of pregabalin.

Naturally, as the proportion of first gabapentinoid prescriptions attributed to OA and licensed or unlicensed indications increased in the more sensitive time windows used, the proportion of prescriptions that were unattributed fell. 77.1% of first prescriptions remained unattributed in window 1, compared to 54.8% in window 2 and 45.8% in window 3 (Table 5.13).[28]

Table 5.13 Number, Percentage and 95% Confidence Intervals of Unattributed First Gabapentinoid Prescriptions in Patients with OA, by Time Window

Window	Definition	Number	% (95% CI)
1	-14d→G→+90	27,022	77.1 (76.7, 77.6)
2	-180d→G→+180	19,198	54.8 (54.3, 55.3)
3	-365d→G→+180	16,042	45.8 (45.3, 46.3)

d: days, G: gabapentinoid

[28] Again, the proportion of unattributed prescriptions during window 4 was not analysed as this time window incorporated a patient's initial OA diagnosis, and therefore the number of unattributed prescriptions would be zero.

The proportion of unattributed first gabapentinoid prescriptions was similar in males and females in windows 1 and 2, although males did have a higher proportion of unattributable prescriptions in window 3. The proportion of unattributed prescriptions remained fairly constant over the study period as well as between gabapentin and pregabalin.

The proportion of unattributed prescriptions was lowest in those aged 40-49 years and highest in patients aged 80 years or older in all time windows studied. 32.8% of first gabapentinoid prescriptions were unattributed to OA or licensed or unlicensed indications in window 3 in those aged 40-49 years, compared to 49.7% of first prescriptions in the oldest age group. The proportion of unattributed prescriptions was highest in Wales in all time windows studied.

5.3 Summary

Based on the primary attribution analysis, over the course of the study period 9.4% of first gabapentinoid prescriptions issued to patients with OA could be attributed to OA, with no evidence of other indications. An additional 13.4% of first prescriptions could be attributed to licensed or unlicensed indications. Of the identified indications, neuropathic pain was the most common cause of attribution. In all time windows studied, the proportion of first prescriptions attributed to OA or to a licensed or unlicensed indication was similar between genders, regions, calendar years and gabapentinoid type. Those aged 40-49 years had the lowest proportion of first gabapentinoid prescriptions that were unattributed to OA or a licensed or unlicensed indication. Despite expansion of the time window studied in the following sensitivity analyses, a large number of first gabapentinoid prescriptions (16,042

(45.8%) in window 3) remained unattributed to OA or to the other identified licensed and unlicensed indications.

6 Discussion

6.1 Summary of Key Findings

The hypothesis of the research presented in this thesis was that the marked rise in the number of gabapentin and pregabalin (gabapentinoid) prescriptions issued within the UK has been driven, in part, by increased off-label prescribing for common painful conditions. Furthermore, there is anecdotal evidence that the gabapentinoids may be being used for the joint pain experienced by patients with OA. The purpose of this thesis was to examine the specific role of osteoarthritis in the increasing numbers of gabapentinoids prescribed in the UK. To investigate this, I explored the possible rationale for and efficacy of their use in OA by conducting a series of scoping reviews of the published literature regarding the gabapentinoids and the epidemiology and current management of OA. I then undertook an original analysis to explore this hypothesis using the CPRD, an electronic UK primary care dataset.

Literature reviews demonstrated that OA is a highly prevalent condition, which has a large impact on patients, health services and wider society. The relevance of this high prevalence and presentation to health services is that even a small proportion of patients prescribed a gabapentinoid would result in a large number of prescriptions being issued, and could thus contribute to the observed increase in prescribing. The undertaking of scoping reviews highlighted that reasons for gabapentinoid prescribing in OA may include the concerns of clinicians with the currently recommended treatment options. Another factor may be the growing body of literature suggesting that some patients with OA may have central

mechanisms contributing to their pain, which can result in features of neuropathic pain, for which the gabapentinoids are recommended.

To date, there have been four randomised controlled trials of the gabapentinoids in patients with OA, each with fewer than 100 participants. The first trial was conducted by Ohtori et al. (2013), who demonstrated that a combination of pregabalin and an NSAID in patients with knee OA was more effective than either as monotherapy by the end of the four week study period. Since then, there has been a 13 week trial of pregabalin in hand OA (Sofat et al., 2017), which demonstrated that pregabalin was more effective than duloxetine compared to placebo, and two trials of knee OA with evidence of a neuropathic component (Filatova et al., 2018; Wright et al., 2017). In the trial conducted by Wright et al. (2017), pregabalin was more effective than paracetamol at 28 days. Although the five week trial by Filatova et al. (2018) demonstrated that patient's pain and function scores improved with pregabalin, no between-group outcomes were reported. As all trial data is currently limited to small trials with short periods of follow-up, there is very limited evidence of the long-term efficacy of the gabapentinoids in OA. On the contrary, there has been an increasing awareness of the risks associated with gabapentinoid use. Whilst adverse effects have increasingly been reported by studies, there are serious concerns with their potential to be misused and diverted, and the number of gabapentinoid-related overdoses and deaths has risen substantially. These concerns have culminated in the likely implementation of the control of gabapentinoid prescribing, and this proposal is currently under review.

My original analysis of UK primary care electronic health records, using the CPRD, estimated that between 1995 and 2015 the age-standardised number of patients with OA receiving their first gabapentinoid prescription increased from less than one per 1,000 person-years to over 27 per 1,000 person-years. Over the course of the study period, the increase in rate of first gabapentinoid prescriptions was observed in all stratifications. However, higher rates of first gabapentinoid prescriptions were observed in females, younger patients, patients who had more recently received their initial OA diagnosis, and those in the North of England, Scotland and Northern Ireland.

The majority (77.1%) of first gabapentinoid prescriptions to patients with OA were not attributed to OA or other identified licensed or unlicensed indications. 10.4% of first gabapentinoid prescriptions could be attributed to OA, although a more cautious estimate of first prescriptions attributable to OA may be 9.4%, once prescriptions in patients with Read codes of licensed or unlicensed indications were attributed to these conditions. The proportion of first gabapentinoid prescriptions attributed to OA remained fairly constant throughout the study period. Prescriptions were more commonly attributed to OA in younger patients. 13.4% of patients prescribed a first gabapentinoid had at least one licensed or unlicensed indication. The proportion of first prescriptions attributed to OA or other licensed or unlicensed indications did increase as the time window around prescription was expanded. However, a large number of first prescriptions did remain unattributed.

6.2 Comparison to Current Literature

The analysis of this study has built on knowledge provided by prior literature of OA and gabapentinoid prescribing, whilst also contributing novel information.

Firstly, the cohort of patients used in this analysis is comparable to previous literature of OA using the CPRD. The proportion of patients who received an OA diagnosis (based on a definitive OA Read code) that were female was very similar to a prior study of the CPRD during the period 1992-2013 (Yu et al., 2017). The earlier, albeit overlapping, time period used in this study may explain the different total number of cases identified and the slight difference in average age at diagnosis compared to the analysis in this thesis, reflecting a slight change in the use of the diagnostic Read code of OA by clinicians over time. Indeed, it should be highlighted that the absolute number of patients identified as incident cases, for instance by year or region, is not necessarily indicative of the incidence of OA, rather it portrays the number of patients given a code of diagnostic OA in the CPRD, which can be affected by the number of practices contributing data (which has decreased from a peak of 597 in 2008 and 2009 to 433 in 2015, displayed in Appendix 3.2 on page 199). Another factor in the number of incident OA cases identified is the behaviour, in terms of the Read codes used, of the practitioners in practices contributing data to the CPRD. It has been demonstrated by prior studies that the incidence of OA has continued to increase, and is expected to continue doing so, but there appears to have been a gradual shift away from the use of diagnostic OA Read codes in the CPRD (Yu et al., 2017, 2018). This may also explain why, in sensitivity analyses, there was a slight decrease in the attribution of first gabapentinoid prescriptions to OA over the course of the study period, particularly from 2008 onwards. This would therefore render the proportions of first prescriptions attributed to OA in more recent years as conservative estimates.

This analysis of gabapentinoid prescribing, although in a cohort of patients with OA, contributes new information to the understanding of gabapentinoid prescribing in relation to prior studies. Whilst the dependence forming medications report (Cartagena et al., 2017) and the study of gabapentinoid use prior to arthroplasty in Australia (Inacio et al., 2018) included the prescribing of gabapentin, in both instances it was studied as part of a group of medications (with lamotrigine as GABAergic medications and amitriptyline as neuropathic pain drugs, respectively). As a result, to the best of my knowledge, this analysis was the first to explore the individual trends in gabapentin prescribing, as prior drug utilisation studies have only studied pregabalin (Asomaning et al., 2016; Viñas-Bastart et al., 2017). Compared to these two studies, the analysis within this thesis also provides a longer study period and a more up-to-date investigation of gabapentinoid prescribing compared to the 2014 cross-sectional study design of the Catalonian study (Viñas-Bastart et al., 2017) and the 6-year study of the THIN database which concluded in 2009 (Asomaning et al., 2016). The nature of this incidence analysis also means it can provide an indication of the risk of a patient with OA receiving a gabapentinoid, both over calendar time and for instance by a patient's age, and this has not been reported previously.

The higher rates of first gabapentinoid prescriptions in younger patients with OA in this study cohort (those aged 40-49 years), have also been documented by a study of opioid prescribing in OA conducted in the US (DeMik et al., 2017). Possible reasons for the higher rate of initiation of pharmacological options such as opioids and the gabapentinoids in those aged 40-49 may include fewer safety concerns in this group of patients due to lower rates of comorbidities and the associated reduction in the concomitant prescribing of other medications. This group of patients may also have increased expectations, potentially linked to a possible loss of quality of life or employment. Furthermore, clinicians may be

reluctant to suggest surgical options in such young patients, due to the current average longevity of prostheses. As this was an analysis of incident prescribing, if every member of the study cohort were to receive their initial OA code aged younger than 45 years and their first gabapentinoid within five years of this date, this could explain a higher rate in this age group and lower rates in subsequent age groups (i.e. depletion of susceptibles). However, this cohort was open to recruitment from a dynamic population (patients registered with general practices contributing to the CPRD), and the median age when a cohort member entered the study due to receiving their first diagnostic OA Read code was 66.0 years.

This was the first analysis of incident gabapentinoid prescribing. However, the higher likelihood of females with OA receiving a first gabapentinoid prescription is comparable to the higher proportion of females prescribed pregabalin in the cross-sectional Spanish study (Viñas-Bastart et al., 2017), providing rates of discontinuation are equal between genders. Females tend to have higher rates of prescribing in all classes of medications compared to males, including pain medications in those aged 40-44 years (Roe et al., 2002). Higher rates of prescribing in females has also been reported in both NSAID use in OA (Dominick et al., 2003) and opioids in chronic non-cancer pain (Campbell et al., 2010). The higher incidence rates of prescribing in females may be due to an increased willingness to take medications and higher expectations, which are potentially reflected in their higher consultation rates compared to males (Hobbs et al., 2016). The higher rate of first gabapentinoid prescriptions in females remained following age-standardisation, and thus a different age distribution of patients with a diagnostic Read code of OA does not account for the increased rate. The attribution analysis demonstrated that the higher incidence of first gabapentinoid prescriptions in females is not accounted for by higher rates of comorbidities that are licensed or unlicensed indications for the gabapentinoids. The fairly constant rate ratio

between the two genders demonstrates that although the rate of first gabapentinoid prescriptions in females has not increased compared to males on a multiplicative scale, the absolute risk difference of a woman with OA receiving her first gabapentinoid has increased, particularly in the period 2010-2014.

The regional variation of first gabapentinoid prescriptions in this cohort of patients with OA has also been noted by other literature and reports of the gabapentinoids. Public Health England, in their 2014 'Advice for prescribers' document, reported that there was a higher number of gabapentin and pregabalin items prescribed in the North of England. This higher rate of prescribing compared to the Midlands or South of England was not felt to be due to social or demographic factors alone (Public Health England, 2014). The dependence forming medications report demonstrated that the proportion of gabapentin, pregabalin and lamotrigine prescriptions that are short versus long term varied greatly in the North East of England. Although this discrepancy may reflect a misclassification in short and long term prescribing, it appears that patients in the North East of England were less likely to be prescribed a gabapentinoid long-term than in other regions in England (Cartagena et al., 2017). Whilst this may be due to differences in the OA population versus those with any condition prescribed a dependence forming medication, it is possible that these differences are due to incidence versus prevalence prescribing analysis. It is possible that within the North East there are a large number of patients that receive gabapentinoids (and thus the incidence rate in the analysis in this thesis was high), but do not remain on them for long periods of time, and therefore this region has a relatively low average length of prescribing (Cartagena et al., 2017). The higher rates of prescribing in the North of England compared to the South have also been reported in opioid studies. Published in 2018, a study of prescribing in England found that nine out of the ten Clinical Commissioning Groups (CCGs)

with the highest rates of prescribing (based on opioid dose per head) were based in the North of England (Mordecai et al., 2018).

Whilst the region-level estimates presented in this thesis were not age or sex-standardised, there did not appear to be large differences between the distributions of the different regions' populations. Analysis at an individual practice or practitioner level was not performed in this analysis due to concerns regarding increasingly small cell sizes, although it is possible that the higher rates of prescribing in certain areas are driven by certain practitioners, practices or areas. This may particularly be the case in the North East of England. As of July 2013, the number of practices in this region was low in comparison to other areas (Herrett et al., 2015). Whilst the number of practices within the UK contributing to the CPRD has since increased (The Farr Institute, 2017), it is not clear how well the North East is currently represented. This lack of practices may be a source of selection bias if those contributing data to the CPRD during the study period were not representative of the wider region, for instance if practices in the CPRD were more (or less) likely to prescribe a gabapentinoid.

The use of gabapentinoids post-operatively following a patient's arthroplasty has been explored by previous literature (Fabritius et al., 2017; Li et al., 2017). Gabapentin or pregabalin may be used in this context either as an analgesic in the immediate post-operative phase or for the iatrogenic neuropathic pain induced by the procedure. However, of the 35,031 patients prescribed a gabapentinoid in the CPRD, 557 (1.6%) patients received their prescription during the one year period following their total knee arthroplasty and therefore this does not seem to represent a substantial proportion of their use in this study. 1,331 (3.8%) patients received their first gabapentinoid (as documented in primary care records) following their procedure. In these cohort members who received

their first gabapentinoid following their TKA, the median time between the procedure and their first gabapentinoid prescription was 2.9 (IQR: 1.2, 5.4) years.

The attribution analysis performed within this thesis also contributes to prior understanding of gabapentinoid prescribing. The dependence forming medications report and the cross-sectional study of pregabalin prescribing in Catalonia, Spain, did present common diagnoses of patients who are prescribed a gabapentinoid. However, as the report only presented groups of diagnoses, such as 'pain', it was not possible to understand the contribution of individual conditions, such as OA, or to appreciate the proportion of off-label prescribing, as neuropathic pain is a licensed indication (Cartagena et al., 2017). Equally, whilst the study of pregabalin prescribing in Catalonia did present the proportion of patients with specific conditions, such as fibromyalgia or epilepsy, a common diagnosis featured in the health records of patients prescribed pregabalin was 'bone and joint pain'. The conditions accounting for this diagnosis were not presented and therefore, again, it was not possible to appreciate the individual contribution of conditions such as OA.

The analysis of the THIN dataset did include attribution of pregabalin prescriptions by individual conditions. However, the analysis in this thesis builds on this prior work by also assessing the proportion of first prescriptions attributed to unlicensed indications. The differences in the proportion of first prescriptions attributed to licensed indications between this work and the THIN study may be due to the different populations and time periods studied, but are most likely due to the techniques used, particularly in the sensitivity analyses. For instance the 61.1% of prescriptions that could not be attributed to a licensed indication in their primary analysis rapidly reduced when these analyses were performed. The classification of all back pain in patients prescribed pregabalin as neuropathic, as performed in their sensitivity analyses, could be viewed as extreme, as back

pain is a common cause of patients presenting to primary care, and it is known that only a small minority of these patients display features of neuropathic pain (Enthoven et al., 2013). Another factor resulting in different attribution estimates between the THIN study and the analysis within this thesis may be that all authors of the study are employees of Pfizer, and thus may have had a conflict of interest to conclude that prescribing was in line with recommendations (Asomaning et al., 2016).

In summary, the analyses presented within this thesis contribute novel information to the current understanding of gabapentinoid prescribing. This work provides an original contribution exploring the incidence of gabapentinoid prescribing among patients with a common painful condition for which their use would be off-label, in which the role of a neuropathic pain component is unclear and for which there is limited efficacy. The stratifications of the incidence rate in this cohort provide a new depth of understanding of gabapentinoid prescribing in this population of patients. The analysis also has consistencies with prior work of OA in the CPRD and prior research of the gabapentinoids, as well as other dependence forming medications, such as opioids.

6.3 Strengths and Limitations

A full understanding of the results contributed by this thesis, including their interpretation and potential implications, requires an appreciation of the study's strengths and limitations.

The predominant strengths of this study originate with the dataset used. The CPRD is a large, UK-wide database that provided a substantial number of events and person-time for the analysis of incident gabapentinoid prescribing in the OA population. Due to the design

of the software used by general practitioners, coding of prescriptions is an automated procedure and therefore the number of gabapentinoids identified in this cohort should be accurate. Secondly, Read codes used in this study have been used in prior studies, whenever possible.

The potential limitations of this analysis are those related to the data and design of analyses. Whilst the CPRD was representative of the 2011 UK census in mid-2013 (Herrett et al., 2015), it is possible that this is no longer the case. Possible reasons for this may include the gradual shift of practices from the VISION software system to EMIS, resulting in them no longer contributing data to the CPRD GOLD dataset. Specific to this study, this shift would have had to affect the incidence of gabapentinoid prescribing or the attribution of first prescriptions. Whilst this seems unlikely, it is possible, for instance if practices that have moved to the newer system are more likely to provide Read codes alongside prescriptions. Another limitation with the choice of using the CPRD is the potential lack of secondary care information. Whilst the majority of prescriptions initiated in secondary care will feature in the CPRD, especially if they are repeat prescriptions, there is the potential for some prescriptions to be missed. As most consultations for OA occur in primary care within the community (Peat et al., 2001), this potential limitation should affect only a small number of gabapentinoid prescriptions prescribed to a patient for OA. However, it is important to be aware of such potential limitations, especially for the number of first prescriptions attributed to other conditions (if they are commonly treated in secondary care), and the number of gabapentinoid prescriptions issued acutely after arthroplasty. However, linkage of the CPRD to secondary care data may not have had a pronounced effect. Whilst the benefit of secondary care data linkage to the CPRD has been demonstrated for identifying acute hospitalisations (Rothnie et al., 2016) and mortality

following venous thromboembolism (Gallagher et al., 2016), linkage is less useful for more chronic conditions such as hepatic injury (Wing et al., 2016).

Another limitation of the CPRD is the ability to assess dosages and adherence. Whilst dose and prescription length are included in the CPRD, patients may be advised to taper their dose by changing the number of tablets taken daily, as recommended by NICE (National Institute for Health and Care Excellence, 2013). As a result the analysis of dosage and duration of prescription may not be an accurate representation of real-world practice. Secondly, it is not possible to understand how patients are taking these medications (regular versus as and when required (PRN)), or whether they are taking the gabapentinoids at all. This lack of adherence may reduce the risks of potential dependence in these patients, but raises concerns regarding the possibility of the diversion of unused gabapentinoids.

Limitations of this research may also arise from the OA population used in this study. Firstly, it is known that patients who receive a Read code of diagnostic OA differ from the large number of patients who are recorded using 'clinical OA' Read codes. The decision was made to use the diagnostic definition to increase the likelihood that cohort members would have the condition (i.e. minimise false-positives). The use of 'clinical OA' Read codes, such as 'joint pain', may also have made distinguishing between OA and other conditions used in the attribution analysis (for instance fibromyalgia), more challenging. However, prior studies have demonstrated that the diagnostic definition is more likely to be used in older patients and those with more severe disease (Jordan et al., 2016). The median age of 66.0 years at time of index OA diagnosis reinforces this. Firstly, this indicates the need for caution when attempting to generalise the findings to all patients presenting with OA to primary care in the UK. Secondly, it is important not to interpret the time since index OA

diagnosis as being the duration of symptomatic disease. As patients tend to be older than those managed under clinical OA Read codes, this may explain the short period of time between a cohort member's initial OA diagnosis (using this definition) and their first gabapentinoid prescription. Indeed, this does not solely apply to pharmacological management such as the gabapentinoids, as the time between initial OA diagnosis and arthroplasty is also much shorter than one would expect if the onset of disease was the initial presentation of symptoms (Yu et al., 2017). Use of the diagnostic definition of OA may have also affected the age-stratified analyses, if more severe disease is a risk factor for receiving a gabapentinoid. Although one may expect that older patients would be more likely to receive their first prescription due to also having high levels of disease severity, the risk in the older age groups may have been diluted by those patients who receive their code of definitive OA due to being older but, due to low disease severity, are not at risk of receiving a gabapentinoid. In contrast, the reason for younger patients receiving a code of definitive OA may be purely due to disease severity, and as a result the incidence rates observed in younger patients may be higher than those of older ages. It should also be noted that, as the diagnostic definition is often recorded for patients with more severe disease, this may be used as the justification for the prescription of a gabapentinoid, resulting in relatively low rates of prescribing in those with clinical OA. However, as almost four times as many patients receive an initial diagnosis of clinical OA compared to those that receive a diagnosis based on the presence of a diagnostic Read code (Yu et al., 2017), a low rate of prescribing may still result in a large absolute number of prescriptions.

The exclusion of patients with prevalent disease may be criticised as limiting generalisability to all OA consulters. However, the design of a fixed cohort with recruitment open across 21 years inevitably means that follow-up (median: 5.1 years) spanned several

years after diagnosis. Whilst patients included in a certain year of the study can be viewed as cases with either incident or prevalent OA during that calendar year, patients who consulted in the first three years of the study period would have been excluded if they also had a Read code of diagnostic OA in the three year period prior to the study period beginning. As a result there may have been patients with OA not included in this cohort study, although one could expect this to be a very small minority. Other patients not included in this analysis (as demonstrated by Figure 3.1 in Chapter 3) include those with prevalent disease who did not receive a diagnostic OA code during the study period, either due to not consulting or due to the choice of codes used by the practitioner. As patients who receive codes of clinical OA tend to have milder disease, and the same could be assumed of those who do not regularly consult, the incidence rate of gabapentinoid prescriptions in patients with OA found in this study may not be representative of all patients with the condition. As a result, the figures can be viewed as more representative of the OA population who receive a diagnostic Read code of OA, and who consult at least once during a 20 year period.

It is possible that the length of the study period used may also be a limitation if patients received their gabapentinoid prescription more than 20 years after their initial diagnosis, although the age-stratified and time since diagnosis results mean that this is unlikely be the case. Equally, as patients were often censored from the cohort due to other criteria, such as deregistering from their practice, expansion of the study period using the existent design is unlikely to significantly alter the number of incident gabapentinoid prescriptions identified. Due to the structure of the CPRD, the incidence rate of gabapentinoid prescribing was not assessed by specific joint sites. It is also therefore possible that a patient with OA of a certain joint was excluded, irrespective of whether they since

developed OA at a different joint site. The use of arthroplasty as exclusion criteria could also be viewed as a potential limitation. Arthroplasty was used to identify prevalent disease, as this is a common endpoint for patients with severe OA, and OA represents the most common indication for both hip and knee arthroplasty (National Joint Registry, 2017). However, it is possible that the patient since developed OA in another joint, or that they were excluded erroneously if the procedure was not for OA, and instead was for another indication, such as a hip fracture.

The method used to attribute gabapentinoid prescriptions has limitations, partly imposed by the nature of the data and coding behaviour in general practice, and partly related to the potential for misclassification of morbidities using Read codes. The technique for attributing prescriptions, including the corresponding sensitivity analyses, was felt to be the best way to attribute prescriptions to indications in electronic health records such as the CPRD, and had been used by prior studies (Asomaning et al., 2016; Bedson et al., 2016). It is clear that practitioners have reasons to prescribe gabapentinoids to patients with OA, due to the condition itself or comorbidities. Limitations of the method used to attribute gabapentinoid prescriptions may arise due to either an under-recording of the identified possible indications, including OA, or due to a failure of the study design to identify all possible indications and their respective Read codes. For instance, whilst all patients with a diagnostic Read code of OA were included in this cohort, a gabapentinoid prescription would not have been attributed to OA if the condition was subsequently recorded using more clinical codes, even if OA was their only morbidity. As a result an unknown proportion of the unattributed prescriptions may be attributable to OA due to clinical OA codes being used around the time of first prescription, rendering this estimate conservative. Equally, although all Read codes of identified indications were previously used codes and from

validated code lists whenever feasible, it is possible that, much like OA, conditions are coded using different terms. An example may include generalised anxiety disorder being recorded more generally as anxiety. Use of free text from a patient's electronic health record may have provided more information regarding diagnoses, as approximately 40% of information can be recorded this way rather than as Read codes. Unfortunately however this is an expensive, complex method and free text data is not available from 2013 onwards (Price et al., 2016).

It was decided that all identified indications should be included in the analyses, and whilst the lack of attribution to certain conditions may have been predicted, particularly in this age group of patients, all possible indications were included to gain the greatest understanding of the use of the gabapentinoids in patients with OA. Whilst this study has assessed the use of the gabapentinoids in OA, a common source of pain, they could equally be used in other, unidentified, painful conditions not mentioned in the reviewed literature, such as back pain. If the gabapentinoids are being used in this condition for neuropathic pain, such as in sciatica, then one could assume that the prescriptions in these patients would be attributed to this licensed indication. There may however be use in patients with no neuropathic pain, resulting in the number of first prescriptions left unattributed being an overestimate.

Other limitations of this method resulting in a conservative figure of the proportion of first prescriptions attributed to OA may be that the presence of a comorbidity Read code may not equate to the first gabapentinoid being used purely for this condition. For instance if a patient with both epilepsy and OA were to be prescribed a gabapentinoid, their OA may be a factor in the clinician's decision to prescribe. Equally, prescriptions attributed to

neuropathic pain may have been a result of neuropathic pain features arising as a consequence of the patient's OA.

In conclusion, this analysis demonstrated that approximately 9-10% of first gabapentinoid prescriptions in patients with OA are attributable to the condition. However, due to potential limitations with the approach to attribute a first gabapentinoid prescription to OA, it is likely that, whilst some prescriptions may have been used for other conditions, such as back pain, there is an unknown proportion of unattributed prescriptions that were also prescribed for OA. This would therefore result in the current estimate being conservative.

6.4 Implications

In light of the study's strengths and limitations, areas of this work may need to be viewed as cautious estimates. However, the analysis in this thesis is a basis of work for future research and has implications for clinicians and policy makers.

One could argue that the fairly constant proportion of first prescriptions attributed to OA compared to the increasing incidence rates in this population may point to OA not being responsible for their use in this condition. However, it is important to highlight that, irrespective of the proportion, the absolute number of first prescriptions attributed to OA (and no other licensed or unlicensed indication) increased from 6 in 2000 to 191 in 2007 and to 454 in 2014. Possible reasons for the steady proportion of first prescriptions attributed to OA may be that the gabapentinoid was prescribed due to rationale that has not recently changed. For instance, based on studies included in the 2017 systematic review, the first articles assessing for the presence of neuropathic pain features in OA were

published in 2011 (French et al., 2017). With the latest NICE guidelines for the management of neuropathic pain being published in 2013 (National Institute for Health and Care Excellence, 2013), an increase in the proportion of first prescriptions attributed to OA may have been expected to increase around this time if this was a factor in their use. Equally, as concerns with the safety of medications such as paracetamol have increased in recent years, it seems more likely that the gabapentinoids are being used for OA due to the lack of efficacy of the currently recommended medications, which one may suspect has always posed an issue for clinicians, leading them to resort to non-guideline medications, such as the gabapentinoids. Due to the predicted increase in the absolute number of patients with OA, clinicians will increasingly be required to manage the pain arising due to the condition. There will, consequently, be a larger number of patients who do not respond to, or are not suitable for, the currently recommended therapies. Unless changes are made to the current guidelines, clinicians may increasingly rely on medications such as the gabapentinoids. However, limited evidence of the efficacy of the off-label use of the gabapentinoids in OA, coupled with severe concerns with their potential risks, means that their use requires careful justification. It should, however, be acknowledged that whilst it is easy to highlight the concerns with the use of medications such as paracetamol, NSAIDs and the gabapentinoids, this leaves clinicians with very few options to treat patients who have increasing expectations. It is critical therefore that raising concerns does not simply push clinicians from one pharmacological option to another, particularly problematic whilst potentially effective non-pharmacological and core treatments, such as exercise, remain inaccessible and underfunded.

The decreasing use of the diagnostic code of OA, as reported by Yu et al. (2017, 2018), may also be a factor in the flat trend observed in the proportion of first prescriptions attributed

to OA. Whilst this decrease in use will also have affected recruitment into the cohort, the median time of 3.4 years between a patient's index date and them receiving their first gabapentinoid demonstrates that these events may occur amid different rates of use of the diagnostic codes of OA. As a result, a gabapentinoid prescribed for the patient's OA pain may have not been coded or coded using more clinical OA codes such as joint pain, resulting in a conservative estimate of attribution to OA, and a relatively flat trend in attribution compared to the increasing incidence rate of gabapentinoid prescribing in the condition.

The difference in the proportion of first gabapentinoid prescriptions attributed to OA (almost three times larger in window 3 compared to window 1) as well as the identified licensed or unlicensed indications in the sensitivity analyses has further demonstrated the effect the time window chosen can have on the results of studies using electronic healthcare databases. Furthermore, with approximately 45% of first prescriptions remaining unattributed even in window 4, a window one could classify as an extremely sensitive time period to identify indications in the CPRD, this analysis has highlighted a potential lack of coding by clinicians, an important finding for researchers of similar studies using the CPRD. As discussed, this may be due to limitations of this analysis in identifying the codes used or conditions for which the gabapentinoids are prescribed. However, the apparent lack of coding raises the question whether coding guidelines, such as a code being given upon management changes in chronic conditions, are being adhered to by participating practices. To understand whether this lack of coding is specific to OA or the gabapentinoids requires further work, however researchers should be aware that a potential lack of coding may be responsible for a lack of attribution in similarly designed studies.

Scoping reviews of the literature demonstrate that it is imperative that clinicians are particularly wary of the prescribing of a gabapentinoid to patients with a history of substance use disorders. Equally, patients with access (either prescribed or via diversion) to other sedative medications, including opioids, which are commonly prescribed in OA, should be viewed as high risk – largely due to the potential for synergistic adverse effects. As reported by many trials studying the efficacy of the gabapentinoids, they do appear to confer benefit in some patients, although this does appear to be a small minority. As a result gabapentinoids may prove effective for the pain of some patients with OA. To maximise their potential efficacy, and to reduce risk, it is imperative that the dose of gabapentin or pregabalin is titrated as recommended. A regular review of patients taking gabapentinoids, particularly for off-label conditions, should also be encouraged, with prescriptions stopped if there is no demonstrable evidence of efficacy. Not only is this important to reduce potential harms, but may reduce diversion, as the diversion of opioids is more common in patients that gain no benefit from their use (Han et al., 2017). Finally, whilst it is likely that a proportion of unattributed gabapentinoid prescriptions are due to OA or other comorbidities, it is likely that a large number of prescriptions that were issued to this cohort of OA patients had no associated Read code entered. Clinicians should therefore be encouraged to record their reasoning for the prescription of a gabapentinoid, particularly when prescribing for off-label conditions such as OA.

The novel contribution of this work provides a platform for future research of the gabapentinoids. Firstly, there remains scope for further work using the CPRD to provide further insight into gabapentinoid prescribing in patients with OA. Performing the same analyses in patients with 'clinical OA', as done by prior studies, would provide more sensitivity to the definition used. This may also provide a greater understanding of the

number of gabapentinoid prescriptions issued to the wider population of patients with OA who do not receive a diagnostic Read code. As demonstrated by prior studies, the use of clinical OA as a definition of the disease results in a younger group of patients, who are earlier in their disease progression. This earlier window may allow a greater opportunity to analyse other prescriptions prescribed to patients with OA before they receive their first gabapentinoid, further allowing the exploration of the hypothesis that clinicians resort to the gabapentinoids due to the ineffectiveness of recommended options. Due to the larger number of patients in a cohort of clinical OA, more detailed analysis beyond a region level would also be possible. Rates of gabapentinoid prescribing could be performed at a practice or practitioner level, which would demonstrate whether rates of prescribing are driven by certain areas, practices or individuals.

It should be noted that this study of the CPRD has other research objectives not included in this thesis (presented in the ISAC protocol, Appendix 1.1, page 158). Stratification of the incidence rates of first gabapentinoid prescriptions by socioeconomic class could not be included in this thesis due to the tight deadline of the MPhil for which it was completed and the lapsing of the Institute's CPRD GOLD license during this time. Use of the Index of Multiple Deprivation (IMD), as performed in a study of opioids (Foy et al., 2016), would allow the exploration of the relationship between a patient's deprivation and rates of gabapentinoid prescribing in patients with OA. As noted by Cartagena et al. (2017, p. 11), GABAergic is "slightly more likely to patients living in deprived areas". This may explain some of the variation seen by geographical region. Research objectives in the ISAC protocol separate to the three included in this thesis include rates of opioid co-prescribing in the OA population and a more detailed analysis of gabapentinoid prescribing in the period before and after a patient's arthroplasty.

Studies beyond the analysis in this thesis may also be possible using electronic health records. For instance assessing the significance of factors for a patient receiving a gabapentinoid prescription or having a prescription attributed to OA or a licensed or unlicensed indication using regression analysis would provide further insight by adjusting for confounding. Finally, an alternative approach may be to study the conditions of patients prescribed a gabapentinoid, however, without condition specific information it would not be possible to identify the risk to a patient with a certain condition, such as OA in this study.

As it is imperative for clinicians that the potential efficacy and risks of gabapentinoids can be assessed, further studies of their use are warranted. Whilst trials tend to be small, with short follow-up, the role of different research designs should be explored. An example may include interviewing clinicians or patients. Surveying clinicians may provide a greater understanding of the rationale for the use of the gabapentinoids as well as who initiates the medications. This would not only allow a better understanding of reasons for use (for instance if started in a pain clinic), but would also allow a more targeted approach to reduce gabapentinoid prescribing at the source of initial prescription, if warranted. Questionnaires issued to patients could be used to ascertain whether they take the gabapentinoids as indicated, and the long-term efficacy and harms of their use. The CPRD allows the possibility to survey clinicians or patients, and the dataset could still be used to identify gabapentinoid prescriptions. An interventional study design could also be used, for example to assess the impact of screen notifications on the rate of gabapentinoid prescribing. For instance GPs who are considering the prescription of a gabapentinoid for off-label conditions such as OA could be alerted to the possible risks. However, the likely control of gabapentinoid prescribing probably supersedes this.

This work may also serve as a basis of information to policy makers and others in public health. A crude estimate of the absolute number of patients with OA being started on a gabapentinoid within the UK can be derived by applying the incidence rate of first gabapentinoid prescription from this thesis to the estimated total number of prevalent cases consulting in the UK with osteoarthritis. The seven-year prevalence rate of 651 patients with OA consulting per 10,000 person-years in 2010 (Jordan et al., 2014), applied to the estimated mid-2010 UK population (Office for National Statistics, 2017c), results in an estimate of just over four million patients with OA living in the UK. Applying the 2010 incidence rate of first gabapentinoid prescriptions from this thesis provides an estimate of 72,000 patients with OA receiving a gabapentinoid during this year. Using the proportions of attributed prescriptions in 2010, more than 6,000 of the total number of first prescriptions may be attributed with some confidence to being specifically ***for*** OA. A further 9,000 can be attributed to licensed or unlicensed indications. Such crude estimates give a rough approximation of the likely numbers affected in a calendar year but should be interpreted with caution. Firstly, whilst the regional primary care dataset used to estimate the prevalence of OA has been found to be representative of wider national and international datasets (Jordan et al., 2007), there may be slight differences. Secondly, whilst the population of incident cases used in the analysis in this thesis differs from the prevalence figures provided in this article, patients included in this study of the CPRD in 2010 can be viewed as those with incident and prevalent disease during this year. Although caution is required, the scaling up to the UK population does, however, provide useful information to policy makers and demonstrates that a substantial number of prescriptions (over 55,000) were prescribed to patients with OA but were not attributable to OA or other licensed or unlicensed indications (Table 6.1). Whilst this is a large volume of initial prescriptions, the total number of prescriptions will be greater, and both values will have

increased in recent years, due to the increased incidence rate of gabapentinoid prescribing, and the rise in the number of patients with OA.

Table 6.1 First Gabapentinoid Prescriptions in Patients with OA, Scaled to the 2010 UK Population

	This study of CPRD: 2010	UK Estimates: 2010
Gabapentinoid prescriptions in OA	3,214	72,561
Attributed to OA	277	6,254
Attributed to other indications	415	9,369
Unattributed prescriptions	2,522	56,938

In the context of the possible dependence-forming nature of the gabapentinoids, this analysis of incident prescribing provides useful information. With the exception of the recent report of dependence forming medications (Cartagena et al., 2017), literature commonly presents gabapentinoid prescriptions as the total number of items prescribed. Whilst duration of treatment is important, incidence analysis can provide a greater appreciation of the number of patients newly prescribed and exposed to these medications and their potential risks. Do the concerns surrounding the gabapentinoids, particularly regarding misuse and diversion, result in a drive by policy makers and clinicians to reduce the length of time patients are prescribed them, or to reduce the number of patients who receive them? Using the benzodiazepines (a class of potentially dependence-forming medications) as an example, it would appear that the length of prescribing is a cause for concern in dependence forming medications such as the gabapentinoids as in the early 2000s NICE set targets to reduce the average length of benzodiazepine prescribing (Cartagena et al., 2017). The distinction between the 2015 data in this thesis and the prevalence data further highlights this. The slowing down of the increase in incident gabapentinoid prescribing demonstrated in this thesis differs from the continued increase in total items prescribed within the UK. One interpretation of this discrepancy may be that the increase in the number of patients starting a gabapentinoid has slowed, and as

prevalence has continued to rise, this must therefore be due to an increase in the average length of prescribing. Another influence could be that external factors, such as Public Health England's 'Advice for Prescribers' had a greater impact on unlicensed conditions such as OA compared to other indications. However, caution should be noted with the interpretation of this finding, and further work is required. Firstly, the differences observed may be due to differences between the cohort of patients with OA in this thesis compared to the general population in national prescribing data. Secondly, as this occurred in the last year of the study, it is not possible to fathom whether this is a one-off (potentially linked to the decrease in practices contributing to data CPRD GOLD), or whether this is the start of a longer trend. As a result, further work to assess average duration of prescribing, as well as prescribing rates in future years, repeating these analyses, is required. This is also important to observe the effect the likely implementation of the control of gabapentin and pregabalin prescribing has on prescribing trends within the UK.

Whilst the trends in this thesis can be evaluated against the general increase in prescribing, the distinction between incidence and prevalence data, whereby one must assume that the duration of treatment has remained constant and that each patient would receive only one prescription, is too great to make a meaningful comparison. As a result, the current lack of incident prescribing data for the gabapentinoids across all conditions means that comparing the data in this study to more general trends is challenging. The availability of this data, whilst not only providing an indication of the duration of use of the gabapentinoids, may further illustrate whether use in OA is in-line with or exceeding general trends, which, if the latter, may further point to use for this common condition.

6.5 Conclusion

Between 1995 and 2015, the proportion of patients with diagnosed OA being issued a first gabapentinoid prescription within UK primary care has risen sharply. Approximately 1 in 10 prescriptions appear to be for the control of OA pain, although the reason for many more prescriptions could not be confidently identified, and thus the estimate of OA attribution may be conservative. The off-label use of medicines is common and the rationale for the use of the gabapentinoids for OA pain may include the lack of efficacy with the currently recommended pharmacological therapies, safety concerns with their use, as well as a potential neuropathic component to the pain experienced by patients with OA. However, there is a lack of trial evidence of their efficacy, and given concerns with their potential for misuse and diversion, the prescribing of the gabapentinoids for a condition as prevalent as OA may require more careful justification by clinicians. The likely future implementation of controls on the prescribing of the gabapentinoids may result in changes in practice, and the effects on the management and outcomes of OA should be evaluated.

7 References

Abbott, C. A., Malik, R. A., Van Ross, E. R. E., Kulkarni, J., & Boulton, A. J. M. (2011). Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care*, *34*(10), 2220–2224. https://doi.org/10.2337/dc11-1108

Advisory Council on the Misuse of Drugs. (2016). *Pregabalin and Gabapentin Advice*. Retrieved from https://www.gov.uk/government/organisations/advisory-council-on-the-misuse-of-drugs/about/membership

Allen, K. D., & Golightly, Y. M. (2015). Epidemiology of osteoarthritis: state of the evidence. *Current Opinion in Rheumatology*, *27*(3), 276–283. https://doi.org/10.1097/BOR.0000000000000161

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., … Vollebergh, W. A. M. (2004). Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica*, *109*(s420), 21–27. https://doi.org/10.1111/j.1600-0047.2004.00327.x

Altman, R., Alarcon, G., Appelrouth, D., Bloch, D., Borenstein, D., Brandt, K., … Wolfe, F. (1990). The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis & Rheumatism*, *33*(11), 1601–1610. https://doi.org/10.1002/art.1780331101

Altman, R., Alarcon, G., Appelrouth, D., Bloch, D., Borenstein, D., Brandt, K., … Wolfe, F. (1991). The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis & Rheumatism*, *34*(5), 505–14. https://doi.org/10.1002/art.1780340502

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., … Wolfe, F. (1986). Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. *Arthritis & Rheumatism*, *29*(8), 1039–1049. https://doi.org/10.1002/art.1780290816

Andersen, S., Thygesen, L. C., Davidsen, M., & Helweg-Larsen, K. (2012). Cumulative years in occupation and the risk of hip or knee osteoarthritis in men and women: a register-based follow-up study. *Occupational and Environmental Medicine*, *69*(5), 325–330. https://doi.org/10.1136/oemed-2011-100033

Arden, N., & Nevitt, M. C. (2006). Osteoarthritis: Epidemiology. *Best Practice and Research: Clinical Rheumatology*, *20*(1), 3–25. https://doi.org/10.1016/j.berh.2005.09.007

Arendt-Nielsen, L. (2017). Pain sensitisation in osteoarthritis. *Clinical and Experimental Rheumatology*, *35*(5), S68–S74.

Arthritis Research UK. (2012). *Musculoskeletal Calculator*. Retrieved from https://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/musculoskeletal-calculator.aspx

Arthritis Research UK. (2018). State of Musculoskeletal Health 2018. Retrieved from https://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/state-of-musculoskeletal-health.aspx

Aşkin, A., Özkan, A., Tosun, A., Demirdal, Ü. S., & İsnaç, F. (2017). Quality of life and functional capacity are adversely affected in osteoarthritis patients with neuropathic pain. *The Kaohsiung Journal of Medical Sciences*, *33*(3), 152–158. https://doi.org/10.1016/j.kjms.2016.12.007

Asomaning, K., Abramsky, S., Liu, Q., Zhou, X., Sobel, R. E., & Watt, S. (2016). Pregabalin prescriptions in the United Kingdom: A drug utilisation study of the Health Improvement Network (THIN) primary care database. *International Journal of Clinical Practice*, *70*(5), 380–388. https://doi.org/10.1111/ijcp.12791

Baldwin, D. S., Den Boer, J. A., Lyndon, G., Emir, B., Schweizer, E., & Haswell, H. (2015). Efficacy and safety of pregabalin in generalised anxiety disorder: A critical review of the literature. *Journal of Psychopharmacology*, *29*(10), 1047–1060. https://doi.org/10.1177/0269881115598411

Ballantyne, J. C., Kalso, E., & Stannard, C. (2016). WHO analgesic ladder: a good concept gone astray. *British Medical Journal*, *352*(January), i20. https://doi.org/10.1136/bmj.i20

Bedson, J., Chen, Y., Ashworth, J., Hayward, R. A., Walters, K., Dunn, K. M., & Jordan, K. P. (2016). Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions. *Pain*, *157*(7), 1525–1531. https://doi.org/10.1097/j.pain.0000000000000557

Bedson, J., & Croft, P. R. (2008). The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskeletal Disorders*, *9*, 116. https://doi.org/10.1186/1471-2474-9-116

Bedson, J., Jordan, K., & Croft, P. (2005). The prevalence and history of knee osteoarthritis in general practice: A case-control study. *Family Practice*, *22*(1), 103–108. https://doi.org/10.1093/fampra/cmh700

Benson, T. (2012). The history of the Read Codes: The inaugural James Read memorial lecture 2011. *Informatics in Primary Care*, *19*(3), 173–182. https://doi.org/10.14236/jhi.v19i3.811

Berger, A., Sadosky, A., Dukes, E., Edelsberg, J., & Oster, G. (2012). Clinical characteristics and patterns of healthcare utilization in patients with painful neuropathic disorders in UK general practice: a retrospective cohort study. *BMC Neurology*, *12*(1), 8. https://doi.org/10.1186/1471-2377-12-8

Bernik, M., Sampaio, T. P. A., & Gandarela, L. (2013). Fibromyalgia Comorbid with Anxiety Disorders and Depression: Combined Medical and Psychological Treatment. *Current Pain and Headache Reports*, *17*(9), 358. https://doi.org/10.1007/s11916-013-0358-3

Beswick, A., Wylde, V., Gooberman-Hill, R., Blom, A., & Dieppe, P. (2012). What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open*, *2*(1), e000435. https://doi.org/10.1136/bmjopen-2011-000435

Bhala, N., Emberson, J., Merhi, A., Abramson, S., Arber, N., Baron, J. A., … Yau, F. (2013). Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. *The Lancet*, *382*(9894), 769–779. https://doi.org/10.1016/S0140-6736(13)60900-9

Bhopal, R. (2008). *Concepts of Epidemiology: Integrating the Ideas, Theories, Principles and Methods of Epidemiology* (Second). Oxford University Press.

Blågestad, T., Nordhus, I. H., Grønli, J., Engesæterf, L. B., Ruths, S., Ranhoff, A. H., … Pallesen, S. (2016). Prescription trajectories and effect of total hip arthroplasty on the use of analgesics, hypnotics, antidepressants, and anxiolytics: results from a population of total hip arthroplasty patients. *Pain*, *157*(3), 643–651. https://doi.org/10.1097/j.pain.0000000000000414

Bockbrader, H. N., Wesche, D., Miller, R., Chapel, S., Janiczek, N., & Burger, P. (2010). A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin. *Clinical Pharmacokinetics*, *49*(10), 661–669. https://doi.org/10.2165/11536200-000000000-00000.

Bonnet, U., & Scherbaum, N. (2017). How addictive are gabapentin and pregabalin? A systematic review. *European Neuropsychopharmacology*, *27*(12), 1185–1215. https://doi.org/10.1016/j.euroneuro.2017.08.430

Brandt, K. D., Dieppe, P., & Radin, E. L. (2008). Etiopathogenesis of Osteoarthritis. *Rheumatic Disease Clinics of North America*, *34*(3), 531–559. https://doi.org/10.1016/j.rdc.2008.05.011

Braun, H., & Gold, G. (2012). Diagnosis of Osteoarthritis: Imaging. *Bone*, *51*(2), 278–288. https://doi.org/10.1016/j.bone.2011.11.019.Diagnosis

Business Services Organisation. (2018). Pharmaceutical Statistics. Retrieved June 4, 2018, from http://www.hscbusiness.hscni.net/services/1806.htm

Campbell, C. I., Weisner, C., LeResche, L., Ray, G. T., Saunders, K., Sullivan, M. D., … Von Korff, M. (2010). Age and Gender Trends in Long-Term Opioid Analgesic Use for Noncancer Pain. *American Journal of Public Health*, *100*(12), 2541–2547. https://doi.org/10.2105/AJPH.2009.180646

Cappuzzo, K. A. (2009). Treatment of postherpetic neuralgia: Focus on pregabalin. *Clinical Interventions in Aging*, *4*(1), 17–23. https://doi.org/10.2147/CIA.S3386

Cartagena, F. J., Porter, L., McManus, S., Strang, J., Hickman, M., Reed, K., & Smith, N. (2017). *Prescribing patterns in dependence forming medicines.* Retrieved from http://phrc.lshtm.ac.uk/papers/PHRC_014_Final_Report.pdf

Cascade, E. F., Kalali, A. H., Nihalani, N. D., & Schwartz, T. L. (2008). Treatment of fibromyalgia. *Psychiatry (Edgmont)*, *5*(3), 18–21. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19727297

Casey, J. A., Schwartz, B. S., Stewart, W. F., & Adler, N. E. (2016). Using Electronic Health Records for Population Health Research: A Review of Methods and Applications. *Annual Review of Public Health*, *37*(1), 61–81. https://doi.org/10.1146/annurev-publhealth-032315-021353

Chaplin, S. (2015). Trends in primary care prescribing, 2004–2014. *Prescriber*, *26*(19), 14–18. https://doi.org/10.1002/psb.1390

Chen, A., Gupte, C., Akhtar, K., Smith, P., & Cobb, J. (2012). The Global Economic Cost of Osteoarthritis: How the UK Compares. *Arthritis*, *2012*, 1–6. https://doi.org/10.1155/2012/698709

Chiappini, S., & Schifano, F. (2016). A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. *CNS Drugs*, *30*(7), 647–654. https://doi.org/10.1007/s40263-016-0359-y

Collin, S. M., Bakken, I. J., Nazareth, I., Crawley, E., & White, P. D. (2017). Trends in the incidence of chronic fatigue syndrome and fibromyalgia in the UK, 2001–2013: a Clinical Practice Research Datalink study. *Journal of the Royal Society of Medicine*, *110*(6), 231–244. https://doi.org/10.1177/0141076817702530

Cooper, T. E., Derry, S., Wiffen, P. J., & Moore, R. A. (2017). Gabapentin for fibromyalgia pain in adults. *Cochrane Database of Systematic Reviews*, (1). https://doi.org/10.1002/14651858.CD012188.pub2.www.cochranelibrary.com

CPRD. (2018). CPRD. Retrieved January 26, 2018, from https://www.cprd.com/home

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., … March, L. (2014). The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*, *73*(7), 1323–1330. https://doi.org/10.1136/annrheumdis-2013-204763

Culliford, D., Maskell, J., Judge, A., Cooper, C., Prieto-Alhambra, D., & Arden, N. K. (2015). Future projections of total hip and knee arthroplasty in the UK: Results from the UK Clinical Practice Research Datalink. *Osteoarthritis and Cartilage*, *23*(4), 594–600. https://doi.org/10.1016/j.joca.2014.12.022

Culvenor, A. G., Engen, C. N., Øiestad, B. E., Engebretsen, L., & Risberg, M. A. (2015). Defining the presence of radiographic knee osteoarthritis: a comparison between the Kellgren and Lawrence system and OARSI atlas criteria. *Knee Surgery, Sports Traumatology, Arthroscopy*, *23*(12), 3532–3539. https://doi.org/10.1007/s00167-014-3205-0

Culvenor, A. G., Øiestad, B. E., Hart, H. F., Stefanik, J. J., Guermazi, A., & Crossley, K. M. (2018). Prevalence of knee osteoarthritis features on magnetic resonance imaging in asymptomatic uninjured adults: a systematic review and meta-analysis. *Br J Sports Med*, *0*(10), 1–12. https://doi.org/10.1136/

da Costa, B., Nüesch, E., Kasteler, R., Husni, E., Welch, V., Rutjes, A., & Jüni, P. (2014). Oral or transdermal opioids for osteoarthritis of the knee or hip (Review). *The Cochrane Database of Systematic Reviews*, (9). https://doi.org/10.1002/14651858.CD003115.pub4.www.cochranelibrary.com

da Costa, B., Reichenbach, S., Keller, N., Nartey, L., Wandel, S., Jüni, P., & Trelle, S. (2017). Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *The Lancet*, *390*, e21–e33. https://doi.org/10.1016/S0140-6736(17)31744-0

Daigle, M., Weinstein, A., Katz, J., & Losina, E. (2012). The cost-effectiveness of total joint arthroplasty: a systematic review of published literature. *Best Practice and Research: Clinical Rheumatology*, *26*(5), 1–15. https://doi.org/doi:10.1016/j.berh.2012.07.013.

Daly, C., Griffin, E., Ashcroft, D. M., Webb, R. T., Perry, I. J., & Arensman, E. (2017). Intentional Drug Overdose Involving Pregabalin and Gabapentin: Findings from the National Self-Harm Registry Ireland, 2007–2015. *Clinical Drug Investigation*, 4–11. https://doi.org/10.1007/s40261-017-0616-y

Dean, A., & Sullivan, K. (2018). OpenEpi. Retrieved February 22, 2018, from https://www.openepi.com/Menu/OE_Menu.htm

Dear, J. W., Antoine, D. J., & Park, B. K. (2015). Where are we now with paracetamol? *BMJ (Clinical Research Ed.)*, *351*(1), h3705. https://doi.org/10.1136/bmj.h3705

DeMik, D. E., Bedard, N. A., Dowdle, S. B., Burnett, R. A., McHugh, M. A., & Callaghan, J. J. (2017). Are We Still Prescribing Opioids for Osteoarthritis? *Journal of Arthroplasty*, *32*(12), 3578–3582.e1. https://doi.org/10.1016/j.arth.2017.07.030

Department of Justice. (2004). Warner-Lambert to Pay $430 million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion [Press Release]. Retrieved from https://www.justice.gov/archive/opa/pr/2004/May/04_civ_322.htm

Derry, S., Cording, M., Pj, W., Law, S., Phillips, T., & Ra, M. (2016). Pregabalin for pain in fibromyalgia in adults. *The Cochrane Database of Systematic Reviews*, (9). https://doi.org/10.1002/14651858.CD011790.pub2.www.cochranelibrary.com

Dieppe, P., & Kirwan, J. (1994). The localization of osteoarthritis. *Rheumatology*, *33*(3), 201–203. https://doi.org/10.1093/rheumatology/33.3.201

Dimitroulas, T., Duarte, R. V., Behura, A., Kitas, G. D., & Raphael, J. H. (2014). Neuropathic pain in osteoarthritis: A review of pathophysiological mechanisms and implications for treatment. *Seminars in Arthritis and Rheumatism*, *44*(2), 145–154. https://doi.org/10.1016/j.semarthrit.2014.05.011

Dominick, K. L., Ahern, F. M., Gold, C. H., & Heller, D. A. (2003). Gender Differences in NSAID Use Among Older Adults with Osteoarthritis. *Annals of Pharmacotherapy*, *37*(11), 1566–1571. https://doi.org/10.1345/aph.1C418

Doyle, M., While, D., Mok, P. L. H., Windfuhr, K., Ashcroft, D. M., Kontopantelis, E., … Webb, R. T. (2016). Suicide risk in primary care patients diagnosed with a personality disorder: a nested case control study. *BMC Family Practice*, *17*, 106. https://doi.org/10.1186/s12875-016-0479-y

Driban, J. B., Sitler, M. R., Barbe, M. F., & Balasubramanian, E. (2010). Is osteoarthritis a heterogeneous disease that can be stratified into subsets? *Clinical Rheumatology*, *29*(2), 123–131. https://doi.org/10.1007/s10067-009-1301-1

Dworkin, R., & Kirkpatrick, P. (2005). Pregabalin. *Nature Reviews Drug Discovery*, *4*, 455–456. https://doi.org/10.1038/nrd1756

Edwards, J. J., Jordan, K. P., Peat, G., Bedson, J., Croft, P. R., Hay, E. M., & Dziedzic, K. S. (2014). Quality of care for OA: The effect of a point-of-care consultation recording template. *Rheumatology (United Kingdom)*, *54*(5), 844–853. https://doi.org/10.1093/rheumatology/keu411

Ennis, Z. N., Dideriksen, D., Vaegter, H. B., Handberg, G., & Pottegård, A. (2016). Acetaminophen for Chronic Pain: A Systematic Review on Efficacy. *Basic & Clinical Pharmacology & Toxicology*, *118*(3), 184–9. https://doi.org/10.1111/bcpt.12527

Enthoven, W. T. M., Scheele, J., Bueving, H., Bohnen, A., Peul, W., van Tulder, M., … Luijsterburg, P. (2013). Back Complaints in Older Adults: Prevalence of Neuropathic Pain and Its Characteristics. *Pain Medicine*, *14*, 1664–1672.

European Medicines Agency. (2006). *Summary information on referral opinion pursuant to Article 30 of Council Directive 2001/83/EC for Neurontin and associated names (see Annex I) International Non- Proprietary Name (INN). Gabapentin: Background information.* Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Neurontin_30/WC500009304.pdf

European Medicines Agency. (2009a). *LYRICA. Summary of Product Characteristics*. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000546/WC500046602.pdf

European Medicines Agency. (2009b). *Refusal Assessment Report For Lyrica*. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000546/WC500076177.pdf

Evoy, K. E., Morrison, M. D., & Saklad, S. R. (2017). Abuse and Misuse of Pregabalin and Gabapentin. *Drugs*, *77*(4), 403–426. https://doi.org/10.1007/s40265-017-0700-x

Fabritius, M. L., Geisler, A., Petersen, P. L., Wetterslev, J., Mathiesen, O., & Dahl, J. B. (2017). Gabapentin in procedure-specific postoperative pain management - preplanned subgroup analyses

from a systematic review with meta-analyses and trial sequential analyses. *BMC Anesthesiology*, *17*(1), 1–20. https://doi.org/10.1186/s12871-017-0373-8

Fairhurst, C., Martin, F., Watt, I., Doran, T., Bland, M., & Brackenbury, W. J. (2016). Sodium channel-inhibiting drugs and cancer survival: protocol for a cohort study using the CPRD primary care database. *BMJ Open*, *6*, e011661. Retrieved from http://bmjopen.bmj.com/content/6/9/e011661.abstract

Fan, H., Yu, W., Zhang, Q., Cao, H., Li, J., Wang, J., … Hu, X. (2014). Efficacy and safety of gabapentin 1800 mg treatment for post-herpetic neuralgia: A meta-analysis of randomized controlled trials. *Journal of Clinical Pharmacy and Therapeutics*, *39*(4), 334–342. https://doi.org/10.1111/jcpt.12167

Farmer, D. (2013). *The prescribing and management of Gabapentin and Pregabalin in HM Prisons and Immigration Removal Centres in England*. Retrieved from https://www.sps.nhs.uk/wp-content/uploads/2013/07/Gabapentin20and20Pregabalin20Offender20Health20Audit20Report.pdf

Farr II, J., Miller, L. E., & Block, J. E. (2013). Quality of life in patients with knee osteoarthritis: a commentary on nonsurgical and surgical treatments. *The Open Orthopaedics Journal*, *7*, 619–23. https://doi.org/10.2174/1874325001307010619

Felson, D., Niu, J., Guermazi, A., Sack, B., & Aliabadi, P. (2011). Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. *Annals of the Rheumatic Diseases*, *70*(11), 1884–1886. https://doi.org/doi:10.1136/ard.2011.155119

Felson, D. T., Naimark, A., Anderson, J., Kazis, L., Castelli, W., & Meenan, R. F. (1987). The Prevalence of Knee Osteoarthritis in the Elderly. The Framingham Osteoarthritis Study. *Arthritis & Rheumatism*, *30*(8), 914–918. https://doi.org/10.1002/art.1780300811

Ferket, B. S., Feldman, Z., Zhou, J., Oei, E. H., Bierma-Zeinstra, S. M. A., & Mazumdar, M. (2017). Impact of total knee replacement practice: cost effectiveness analysis of data from the Osteoarthritis Initiative. *BMJ*, *356*, j1131. https://doi.org/10.1136/bmj.j1131

Filatova, E., Turovskaya, E., Alekseeva, L., & Nasonova, V. (2018). Pregabalin Efficacy in Treatment of Chronic Pain in Patients with Knee Osteoarthritis. *Annals of the Rheumatic Diseases*, 2–3. https://doi.org/10.1136/annrheumdis-2018-eular.6036

Filipetto, F. A., Zipp, C. P., & Coren, J. S. (2010). Potential for pregabalin abuse or diversion after past drug-seeking behavior. *The Journal of the American Osteopathic Association*, *110*(10), 605–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21068226

Foy, R., Leaman, B., McCrorie, C., Petty, D., House, A., Bennett, M., … West, R. (2016). Prescribed opioids in primary care: Cross-sectional and longitudinal analyses of influence of patient and practice characteristics. *BMJ Open*, *6*(5). https://doi.org/10.1136/bmjopen-2015-010276

French, H. P., Smart, K. M., & Doyle, F. (2017). Prevalence of neuropathic pain in knee or hip osteoarthritis: A systematic review and meta-analysis. *Seminars in Arthritis and Rheumatism*, *47*(1), 1–8. https://doi.org/10.1016/j.semarthrit.2017.02.008

Freynhagen, R., Baron, R., Gockel, U., & Tölle, T. R. (2006). painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Current Medical Research and Opinion*, *22*(10), 1911–1920. https://doi.org/10.1185/030079906X132488

Freynhagen, R., Serpell, M., Emir, B., Whalen, E., Parsons, B., Clair, A., & Latymer, M. (2015). A comprehensive drug safety evaluation of pregabalin in peripheral neuropathic pain. *Pain Practice*, *15*(1), 47–57. https://doi.org/10.1111/papr.12146

Fu, K., Robbins, S. R., & McDougall, J. J. (2017). Osteoarthritis: the genesis of pain. *Rheumatology*, 1–8. https://doi.org/10.1093/rheumatology/kex419

Fukada, C., Kohler, J. C., Boon, H., Austin, Z., & Krahn, M. (2012). Prescribing gabapentin off label: Perspectives from psychiatry, pain and neurology specialists. *Canadian Pharmacists Journal : CPJ = Revue Des Pharmaciens Du Canada : RPC*, *145*(6), 280–284.e1. https://doi.org/10.3821/145.6.cpj280

Gallagher, A. M., Williams, T., Leufkens, H. G. M., & De Vries, F. (2016). The impact of the choice of data source in record linkage studies estimating mortality in venous thromboembolism. *PLoS ONE*, *11*(2), 1–11. https://doi.org/10.1371/journal.pone.0148349

Giladi, H., Choinière, M., Fitzcharles, M.-A., Ware, M. A., Tan, X., & Shir, Y. (2015). Pregabalin for chronic pain: does one medication fit all? *Current Medical Research and Opinion*, *31*(7), 1403–11. https://doi.org/10.1185/03007995.2015.1040750

Gomes, T., Juurlink, D. N., Antoniou, T., Mamdani, M. M., Paterson, J. M., & van den Brink, W. (2017). Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. *PLOS Medicine*, *14*(10), 1–13. https://doi.org/10.1371/journal.pmed.1002396

Goodman, C., & Brett, A. (2017). Gabapentin and Pregabalin for Pain — Is Increased Prescribing a Cause for Concern? *New England Journal of Medicine*, *377*(5), 411–414. https://doi.org/10.1056/NEJMp1706754

GoodRx. (2017). The GoodRx top 10: September 2017. Retrieved March 15, 2018, from https://www.goodrx.com/drug-guide

Gorton, H., Webb, R., Carr, M., DelPozo-Banos, M., John, A., & Ashcroft, D. (2018). Risk of Unnatural Mortality in People With Epilepsy. *JAMA Neurology*, *Published*. https://doi.org/doi:10.1001/jamaneurol.2018.0333

Gregory, S. (2009). *General practice in England: An overview*. Retrieved from https://www.kingsfund.org.uk/sites/files/kf/general-practice-in-england-overview-sarah-gregory-kings-fund-september-2009.pdf

Gwilym, S. E., Keltner, J. R., Warnaby, C. E., Carr, A. J., Chizh, B., Chessell, I., & Tracey, I. (2009). Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Care and Research*, *61*(9), 1226–1234. https://doi.org/10.1002/art.24837

Hall, G. C., Morant, S. V., Carroll, D., Gabriel, Z. L., & McQuay, H. J. (2013). An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. *BMC Family Practice*, *14*(1), 1. https://doi.org/10.1186/1471-2296-14-28

Hamer, A. M., Haxby, D. G., McFarland, B. H., & Ketchum, K. (2002). Gabapentin use in a managed medicaid population. *J Manag Care Pharm*, *8*(4), 266–271. https://doi.org/10.18553/jmcp.2002.8.4.266

Han, B., Compton, W. M., Blanco, C., Crane, E., Lee, J., & Jones, C. M. (2017). Prescription opioid use, misuse, and use disorders in U.S. Adults: 2015 national survey on drug use and health. *Annals of Internal Medicine*, *167*(5), 293–301. https://doi.org/10.7326/M17-0865

Hauber, A. B., Arden, N. K., Mohamed, A. F., Johnson, F. R., Peloso, P. M., Watson, D. J., … Taylor, S. D. (2013). A discrete-choice experiment of United Kingdom patients' willingness to risk adverse events for improved function and pain control in osteoarthritis. *Osteoarthritis and Cartilage*, *21*(2), 289–297. https://doi.org/10.1016/j.joca.2012.11.007

Herbolsheimer, F., Schaap, L. A., Edwards, M. H., Maggi, S., Otero, Á., Timmermans, E. J., … Peter, R. (2016). Physical Activity Patterns Among Older Adults With and Without Knee Osteoarthritis in Six European Countries. *Arthritis Care & Research*, *68*(2), 228–236. https://doi.org/10.1002/acr.22669

Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., Staa, T. van, & Smeeth, L. (2015). Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International Journal of Epidemiology*, *44*(3), 827–836. https://doi.org/10.1093/ije/dyv098

Herrett, E., Thomas, S. L., Schoonen, W. M., Smeeth, L., & Hall, A. J. (2010). Validation and validity of diagnoses in the General Practice Research Database: A systematic review. *British Journal of Clinical Pharmacology*, *69*(1), 4–14. https://doi.org/10.1111/j.1365-2125.2009.03537.x

Hippisley-Cox, J., & Vinogradova, Y. (2009). *Trends in consultation rates in General Practice 1995/1996 to 2008/2009: Analysis of the QResearch® database.* Retrieved from https://digital.nhs.uk/data-and-information/publications/statistical/trends-in-consultation-rates-in-general-practice/qresearch-report-on-trends-in-consultation-rates-in-general-practices-uk-1995-2008

Ho-Pham, L. T., Lai, T. Q., Mai, L. D., Doan, M. C., Pham, H. N., & Nguyen, T. V. (2014). Prevalence of radiographic osteoarthritis of the knee and its relationship to self-reported pain. *PLoS ONE*, *9*(4), 1–7. https://doi.org/10.1371/journal.pone.0094563

Hobbs, F. D. R., Bankhead, C., Mukhtar, T., Stevens, S., Perera-Salazar, R., Holt, T., & Salisbury, C. (2016). Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007–14. *The Lancet*, *387*(10035), 2323–2330. https://doi.org/10.1016/S0140-6736(16)00620-6

Hochman, J. R., Gagliese, L., Davis, A. M., & Hawker, G. A. (2011). Neuropathic pain symptoms in a community knee OA cohort. *Osteoarthritis and Cartilage*, *19*(6), 647–654. https://doi.org/10.1016/j.joca.2011.03.007

Holbech, J. V., Bach, F. W., Finnerup, N. B., Jensen, T. S., & Sindrup, S. H. (2016). Pain phenotype as a predictor for drug response in painful polyneuropathy - A retrospective analysis of data from controlled clinical trials. *Pain*, *157*(6), 1305–1313. https://doi.org/10.1097/j.pain.0000000000000563

Home Office. (2017). *A consultation on proposals to schedule pregabalin and gabapentin under the Misuse of Drugs Regulations 2001*. Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/666023/Consultation_document_pregabalin_and_gabapentin_for_LAUNCH_revision.pdf

Horsfield, P. (2005). QOF Business Rules v5. Retrieved February 7, 2018, from https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/2/

Iacobucci, G. (2017). UK government to reclassify pregabalin and gabapentin after rise in deaths. *Bmj*, *358*, j4441. https://doi.org/10.1136/bmj.j4441

Inacio, M. C. S., Cashman, K., Pratt, N. L., Gillam, M. H., Caughey, G., Graves, S. E., & Roughead, E. E. (2018). Prevalence and changes in analgesic medication utilisation 1 year prior to total joint

replacement in an older cohort of patients. *Osteoarthritis and Cartilage*, *26*(3), 356–362. https://doi.org/10.1016/j.joca.2017.11.016

Institute for Health Metrics and Evaluation. (2017). Global Health Data Exchange. Retrieved December 6, 2017, from http://ghdx.healthdata.org/gbd-results-tool

ISD Scotland. (2018). Community Dispensing. Retrieved June 4, 2018, from http://www.isdscotland.org/Health-topics/Prescribing-and-medicines/Community-Dispensing/Prescription-Cost-Analysis/

Ivanavicius, S. P., Ball, A. D., Heapy, C. G., Westwood, F. R., Murray, F., & Read, S. J. (2007). Structural pathology in a rodent model of osteoarthritis is associated with neuropathic pain: Increased expression of ATF-3 and pharmacological characterisation. *Pain*, *128*(3), 272–282. https://doi.org/10.1016/j.pain.2006.12.022

Jackson, H., Barnett, L. A., Jordan, K. P., Dziedzic, K. S., Cottrell, E., Finney, A. G., … Edwards, J. J. (2017). Patterns of routine primary care for osteoarthritis in the UK: a cross-sectional electronic health records study. *BMJ Open*, *7*(12), e019694. https://doi.org/10.1136/bmjopen-2017-019694

Jensen, T. S., Baron, R., Haanpää, M., Kalso, E., Loeser, J. D., Rice, A. S. C., & Treede, R. D. (2011). A new definition of neuropathic pain. *Pain*, *152*(10), 2204–2205. https://doi.org/10.1016/j.pain.2011.06.017

Joint Formulary Committee. (2018). British National Formulary (online). Retrieved May 9, 2018, from http://www.medicinescomplete.com

Jordan, K., Clarke, A. M., Symmons, D. P. M., Fleming, D., Porcheret, M., Kadam, U. T., & Croft, P. (2007). Measuring disease prevalence: A comparison of musculoskeletal disease using four general practice consultation databases. *British Journal of General Practice*, *57*(534), 7–14.

Jordan, K., Jöud, A., Bergknut, C., Croft, P., Edwards, J. J., Peat, G., … Englund, M. (2014). International comparisons of the consultation prevalence of musculoskeletal conditions using population-based healthcare data from England and Sweden. *Annals of the Rheumatic Diseases*, *73*(1), 212–218. https://doi.org/10.1136/annrheumdis-2012-202634

Jordan, K. P., Tan, V., Edwards, J. J., Chen, Y., Englund, M., Hubertsson, J., … Peat, G. (2016). Influences on the decision to use an osteoarthritis diagnosis in primary care: A cohort study with linked survey and electronic health record data. *Osteoarthritis and Cartilage*, *24*(5), 786–793. https://doi.org/10.1016/j.joca.2015.12.015

Kapil, V., Green, J. L., Le Lait, M. C., Wood, D. M., & Dargan, P. I. (2014). Misuse of the γ-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. *British Journal of Clinical Pharmacology*, *78*(1), 190–191. https://doi.org/10.1111/bcp.12277

Kaufman, R. (2004). The Neurontin Controversy: The Saga of Off-Label Drug Regulation Continues. *Legal Electronic Document Archive (LEDA), Harvard University.* Retrieved from https://dash.harvard.edu/bitstream/handle/1/8963868/Kaufman.pdf?sequence=1

Khan, N. F., Perera, R., Harper, S., & Rose, P. W. (2010). Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Family Practice*, *11*(1), 1. https://doi.org/10.1186/1471-2296-11-1

Kim, J.-S., Kroin, J. S., Buvanendran, A., Li, X., van Wijnen, A. J., Tuman, K. J., & Im, H.-J. (2011). Characterization of a new animal model for evaluation and treatment of back pain due to lumbar

facet joint osteoarthritis. *Arthritis and Rheumatism*, *63*(10), 2966–73. https://doi.org/10.1002/art.30487

Kohn, M. D., Sassoon, A. A., & Fernando, N. D. (2016). Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. *Clinical Orthopaedics and Related Research*, *474*(8), 1886–1893. https://doi.org/10.1007/s11999-016-4732-4

Kontopantelis, E., Springate, D., Reeves, D., Ashcroft, D. M., Rutter, M. K., Buchan, I., & Doran, T. (2015). Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study. *Diabetologia*, *58*(3), 505–518. https://doi.org/10.1007/s00125-014-3473-8

Krebs, E. E., Gravely, A., Nugent, S., Jensen, A. C., DeRonne, B., Goldsmith, E. S., … Noorbaloochi, S. (2018). Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain. *JAMA*, *319*(9), 872–882. https://doi.org/10.1001/jama.2018.0899

Kwok, H., Khuu, W., Fernandes, K., Martins, D., Tadrous, M., Singh, S., … Gomes, T. (2017). Impact of unrestricted access to pregabalin on the use of opioids and other CNS-active medications: A cross-sectional time series analysis. *Pain Medicine (United States)*, *18*(6), 1019–1026. https://doi.org/10.1093/pm/pnw351

Lane, N., Shidara, K., & Wise, B. (2017). Osteoarthritis year in review 2016: clinical. *Osteoarthritis and Cartilage*, *25*(2), 209–215. https://doi.org/10.1016/j.joca.2016.12.009

Lawrence, J. S. (1977). *Rheumatism in Populations*. London: W.M. Heinemann Medical Books.

Lawson, D. H., Sherman, V., & Hollowell, J. (1998). The General Practice Research Database. *QJM: Monthly Journal of the Association of Physicians*, *91*(6), 445–452.

Lee, Y. C., Nassikas, N. J., & Clauw, D. J. (2011). The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Research & Therapy*, *13*(2), 211. https://doi.org/10.1186/ar3306

Li, F., Ma, J., Kuang, M., Jiang, X., Wang, Y., Lu, B., … Ma, X. (2017). The efficacy of pregabalin for the management of postoperative pain in primary total knee and hip arthroplasty: A meta-analysis. *Journal of Orthopaedic Surgery and Research*, *12*(1), 1–10. https://doi.org/10.1186/s13018-017-0540-0

Litwic, A., Edwards, M. H., Dennison, E. M., & Cooper, C. (2013). Epidemiology and burden of osteoarthritis. *British Medical Bulletin*, *105*(1), 185–199. https://doi.org/10.1093/bmb/lds038

Lix, L., Yogendran, M., & Mann, J. (2006). Defining and validating chronic diseases: an administrative data approach. Retrieved from http://mchp-appserv.cpe.umanitoba.ca/reference/chronic.disease.pdf

Lluch Girbes, E., Duenas, L., Barbero, M., Falla, D., Baert, I. A. C., Meeus, M., … Nijs, J. (2016). Expanded Distribution of Pain as a Sign of Central Sensitization in Individuals With Symptomatic Knee Osteoarthritis. *Physical Therapy*, *96*(8), 1196–1207. https://doi.org/10.2522/ptj.20150492

Loeser, R. F., Collins, J. A., & Diekman, B. O. (2016). Ageing and the pathogenesis of osteoarthritis. *Nature Reviews Rheumatology*, *12*(7), 412–420. https://doi.org/10.1038/nrrheum.2016.65

Louati, K., Vidal, C., Berenbaum, F., & Sellam, J. (2015). Association between diabetes mellitus and osteoarthritis: systematic literature review and meta-analysis. *RMD Open*, *1*, e000077. https://doi.org/10.1136/rmdopen-2015-000077

Loughlin, J. (2015). Genetic contribution to osteoarthritis development. *Current Opinion in Rheumatology*, *27*(3), 284–288. https://doi.org/10.1097/BOR.0000000000000171

Lyndon, A., Audrey, S., Wells, C., Burnell, E. S., Ingle, S., Hill, R., … Henderson, G. (2017). Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction*, *112*(9), 1580–1589. https://doi.org/10.1111/add.13843

Macfarlane, G. J., Kronisch, C., Dean, L. E., Atzeni, F., Häuser, W., Flub, E., … Jones, G. T. (2017). EULAR revised recommendations for the management of fibromyalgia. *Annals of the Rheumatic Diseases*, *76*(2), 318–328. https://doi.org/10.1136/annrheumdis-2016-209724

Machado, G. C., Maher, C. G., Ferreira, P. H., Pinheiro, M. B., Lin, C.-W. C., Day, R. O., … Ferreira, M. L. (2015). Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ: British Medical Journal*, *350*(h1225), 1–13. https://doi.org/10.1136/bmj.h1225

Mack, A. (2003). Examination of the Evidence for Off-Label Use of Gabapentin. *Journal of Managed Care Pharmacy*, *9*(6), 559–568. https://doi.org/10.18553/jmcp.2003.9.6.559

Mallen, C., & Hay, E. (2016). Managing back pain and osteoarthritis without paracetamol. *British Journal of Sports Medicine*, *50*, 1286–1287. https://doi.org/doi:10.1136/bjsports-2015-h1352rep

Manchikanti, L., Helm, S., Fellows, B., Janata, J. W., Pampati, V., Grider, J. S., & Boswell, M. V. (2012). Opioid epidemic in the United States. *Pain Physician*, *15*, ES9-38. https://doi.org/10.1016/j.emc.2015.11.002

Mannan, F., Chaudhry, Z., Gibson-White, A., Syed, U., Ahmed, S., Kousoulis, A., & Majeed, A. (2017). Outputs and Growth of Primary Care Databases in the United Kingdom: Bibliometric Analysis. *Journal of Innovation in Health Informatics*, *24*(3), 942. https://doi.org/10.14236/jhi.v24i3.942

Martin, C., Alcock, N., Hiom, S., & Birchall, J. (2017). Development and Evaluation of Topical Gabapentin Formulations. *Pharmaceutics*, *9*(3), 31. https://doi.org/10.3390/pharmaceutics9030031

Mathur, R., Bhaskaran, K., Chaturvedi, N., Leon, D. A., Van Staa, T., Grundy, E., & Smeeth, L. (2014). Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *Journal of Public Health (United Kingdom)*, *36*(4), 684–692. https://doi.org/10.1093/pubmed/fdt116

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., … Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage*, *22*(3), 363–388. https://doi.org/10.1016/j.joca.2014.01.003

Melzer, D., Tavakoly, B., Winder, R. E., Masoli, J. A. H., Henley, W. E., Ble, A., & Richards, S. H. (2015). Much more medicine for the oldest old: trends in UK electronic clinical records. *Age and Ageing*, *44*(1), 46–53. https://doi.org/10.1093/ageing/afu113

Mesci, N., Mesci, E., & Külcü, D. G. (2016). Association of neuropathic pain with ultrasonographic measurements of femoral cartilage thickness and clinical parameters in patients with knee osteoarthritis. *Journal of Physical Therapy Science*, *28*(8), 2190–5. https://doi.org/10.1589/jpts.28.2190

Monira Hussain, S., Wang, Y., Cicuttini, F. M., Simpson, J. A., Giles, G. G., Graves, S., & Wluka, A. E. (2014). Incidence of total knee and hip replacement for osteoarthritis in relation to the metabolic

syndrome and its components: A prospective cohort study. *Seminars in Arthritis and Rheumatism*, *43*(4), 429–436. https://doi.org/10.1016/j.semarthrit.2013.07.013

Moore, A., & Phillips, C. (1999). Cost of NSAID adverse effects to the UK National Health Service. *Journal of Medical Economics*, *2*(1–4), 45–55. https://doi.org/10.3111/199902045055

Moore, N., Pollack, C., & Butkerait, P. (2015). Adverse drug reactions and drug–drug interactions with over-the-counter NSAIDs. *Therapeutics and Clinical Risk Management*, *11*, 1061–1075. https://doi.org/10.2147/TCRM.S79135

Moore, R., Chi, C.-C., Wiffen, P. J., Derry, S., & Rice, A. S. (2015). Oral nonsteroidal anti-inflammatory drugs for neuropathic pain (Review). *Cochrane Database of Systematic Reviews*, (10), 1–27. https://doi.org/10.1002/14651858.CD010902.pub2.www.cochranelibrary.com

Mordecai, L., Reynolds, C., Donaldson, L. J., & de C Williams, A. C. (2018). Patterns of regional variation of opioid prescribing in primary care in England: a retrospective observational study. *British Journal of General Practice*, *68*(668), e225–e233. https://doi.org/10.3399/bjgp18X695057

Mukhtar, T. K., Bankhead, C., Stevens, S., Perera, R., Holt, T. A., Salisbury, C., & Hobbs, F. R. (2018). Factors associated with consultation rates in general practice in England, 2013–2014: a cross-sectional study. *British Journal of General Practice*, bjgp18X695981. https://doi.org/10.3399/bjgp18X695981

Nahar, L. K., Andrews, R., Murphy, K. G., & Paterson, S. (2017). Misuse of gabapentin and pregabalin may be underestimated. *BMJ*, *359*, j5312. https://doi.org/10.1136/BMJ.J5312

Naing, N. N. (2000). Easy Way to Learn Standardization: Direct and Indirect Methods. *The Malaysian Journal of Medical Sciences: MJMS*, *7*(1), 10–15. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3406211/

Naleschinski, D., & Baron, R. (2010). Complex regional pain syndrome type I: neuropathic or not? *Current Pain and Headache Reports*, *14*(3), 196–202. https://doi.org/10.1007/s11916-010-0115-9

National Clinical Guideline Centre. (2013). *Osteoarthritis: the care and management of osteoarthritis in adults [Draft]*. Retrieved from https://www.nice.org.uk/guidance/cg177/.../osteoarthritis-update-nice-version2

National Institute for Health and Care Excellence. (2013). Neuropathic pain in adults: pharmacological management in non-specialist settings. Retrieved January 15, 2018, from https://www.nice.org.uk/guidance/cg173

National Institute for Health and Care Excellence [NICE]. (2014). Osteoarthritis: care and management. Clinical Guideline [CG177]. Retrieved December 12, 2017, from https://www.nice.org.uk/guidance/cg177

National Joint Registry. (2017). *14th Annual Report*. Retrieved from http://www.njrreports.org.uk/Portals/0/PDFdownloads/NJR 14th Annual Report 2017.pdf

Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and Cartilage*, *21*(9), 1145–1153. https://doi.org/10.1016/j.joca.2013.03.018

Newlove-Delgado, T., Ford, T. J., Hamilton, W., Stein, K., & Ukoumunne, O. C. (2018). Prescribing of medication for attention deficit hyperactivity disorder among young people in the Clinical Practice Research Datalink 2005-2013: analysis of time to cessation. *European Child & Adolescent Psychiatry*, *27*(1), 29–35. https://doi.org/10.1007/s00787-017-1011-1

NHS Digital. (2017). Prescription Cost Analysis Archive. Retrieved January 7, 2018, from https://digital.nhs.uk/pubsearch?q=prescription+cost+analysis&s=s

NHS Digital. (2018). Read Codes. Retrieved May 8, 2018, from https://digital.nhs.uk/services/terminology-and-classifications/read-codes

NICE. (2014). Osteoarthritis: care and management. Clinical Guideline [CG177]. Retrieved December 12, 2017, from https://www.nice.org.uk/guidance/cg177

Niinimäki, T., Eskelinen, A., Mäkelä, K., Ohtonen, P., Puhto, A. P., & Remes, V. (2014). Unicompartmental Knee Arthroplasty Survivorship is Lower Than TKA Survivorship: A 27-year Finnish Registry Study. *Clinical Orthopaedics and Related Research*, *472*(5), 1496–1501. https://doi.org/10.1007/s11999-013-3347-2

Nitika, Mishra, S. S., & Lohani, P. (2017). Lexis Expansion: a prerequisite for analyzing time changing variables in a cohort study. *Nepal Journal of Epidemiology*, *7*(2), 681–684. https://doi.org/10.3126/nje.v7i2.17974

O'Driscoll, S. L., & Jayson, M. I. V. (1974). Pain Threshold Analysis in Patients with Osteoarthrosis of Hip. *British Medical Journal*, *3*(5933), 714–715. https://doi.org/10.1136/bmj.3.5933.714

Office for National Statistics. (2017a). Deaths Related to Drug Poisoning, England and Wales. Retrieved January 17, 2018, from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsrelatedtodrugpoisoningenglandandwalesreferencetable

Office for National Statistics. (2017b). Number of deaths where pregabalin and gabapentin were mentioned on the death certificate, by sex and age, England and Wales, 2016 registrations. Retrieved January 17, 2018, from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007494numberofdeathswherepregabalinandgabapentinwerementionedonthedeathcertificatebysexandageenglandandwales2016registrations

Office for National Statistics. (2017c). Population Estimates for UK, England and Wales, Scotland and Northern Ireland. Retrieved January 15, 2018, from https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland

Office for National Statistics. (2017d). *Sickness Absence in the Labour Market*. Retrieved from https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/labourproductivity/articles/sicknessabsenceinthelabourmarket/2016

Office for National Statistics. (2018). Revised population estimates for England and Wales: mid-2012 to mid-2016. Retrieved May 15, 2018, from https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2012tomid2016

Ogawa, S., Awaga, Y., Takashima, M., Hama, A., Matsuda, A., & Takamatsu, H. (2016). Antinociceptive effect of clinical analgesics in a nonhuman primate model of knee osteoarthritis. *European Journal of Pharmacology*, *786*, 179–185. https://doi.org/10.1016/j.ejphar.2016.06.008

Ohtori, S., Inoue, G., Orita, S., Takaso, M., Eguchi, Y., Ochiai, N., … Takahashi, K. (2013). Efficacy of combination of meloxicam and pregabalin for pain in knee osteoarthritis. *Yonsei Medical Journal*, *54*(5), 1253–1258. https://doi.org/10.3349/ymj.2013.54.5.1253

Østeras, N., Jordan, K. P., Clausen, B., Cordeiro, C., Dziedzic, K., Edwards, J., … Hagen, K. B. (2015). Self-reported quality care for knee osteoarthritis: Comparisons across Denmark, Norway, Portugal and the UK. *RMD Open*, *1*(1), 1–9. https://doi.org/10.1136/rmdopen-2015-000136

Parsons, C., Clynes, M., Syddall, H., Jagannath, D., Litwic, A., van der Pas, S., … Edwards, M. H. (2015). How well do radiographic, clinical and self-reported diagnoses of knee osteoarthritis agree? Findings from the Hertfordshire cohort study. *SpringerPlus*, *4*, 177. https://doi.org/10.1186/s40064-015-0949-z

Paskins, Z., Sanders, T., & Hassell, A. B. (2013). What influences patients with osteoarthritis to consult their GP about their symptoms? A narrative review. *BMC Family Practice*, *14*(12), 195. https://doi.org/10.1186/1471-2296-14-195

Peat, G., McCarney, R., & Croft, P. (2001). Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Annals of the Rheumatic Diseases*, *60*(2), 91–97. https://doi.org/10.1136/ard.60.2.91

Pereira, D., Peleteiro, B., Araújo, J., Branco, J., Santos, R. A., & Ramos, E. (2011). The effect of osteoarthritis definition on prevalence and incidence estimates: A systematic review. *Osteoarthritis and Cartilage*, *19*(11), 1270–1285. https://doi.org/10.1016/j.joca.2011.08.009

Petersen, M. (2008). *Our Daily Meds: How the Pharmaceutical Companies Transformed Themselves into Slick Marketing Machines and Hooked the Nation on Prescription Drugs*. Sarah Crichton Books.

Pfizer. (2016). LYRICA. Highlights of Prescribing Information. Retrieved January 10, 2018, from http://labeling.pfizer.com/ShowLabeling.aspx?id=561

Pinedo-Villanueva, R., Turner, D., Raftery, J., Cooper, C., & Arden, N. (2014). Outcomes after total hip replacement. *Osteoarthritis and Cartilage*, *22*, S214. https://doi.org/10.1016/j.joca.2014.02.410

Price, S. J., Stapley, S. A., Shephard, E., Barraclough, K., & Hamilton, W. T. (2016). Is omission of free text records a possible source of data loss and bias in Clinical Practice Research Datalink studies? A case-control study. *BMJ Open*, *6*(5), 1–7. https://doi.org/10.1136/bmjopen-2016-011664

Prieto-Alhambra, D., Judge, A., Javaid, M. K., Cooper, C., Diez-Perez, A., & Arden, N. K. (2014). Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Annals of the Rheumatic Diseases*, *73*(9), 1659–1664. https://doi.org/10.1136/annrheumdis-2013-203355

Public Health England. (2014). Advice for prescribers on the risk of the misuse of pregabalin and gabapentin, 1–9.

Public Health England. (2017). Musculoskeletal Diseases. Retrieved June 15, 2018, from https://fingertips.phe.org.uk/profile/msk/data#page/11/gid/1938133148/pat/6/par/E12000004/ati/102/are/E06000015/iid/93093/age/251/sex/4

Puig-Junoy, J., & Ruiz Zamora, A. (2015). Socio-economic costs of osteoarthritis: A systematic review of cost-of-illness studies. *Seminars in Arthritis and Rheumatism*, *44*(5), 531–541. https://doi.org/10.1016/j.semarthrit.2014.10.012

Rahman, M. M., Cibere, J., Goldsmith, C. H., Anis, A. H., & Kopec, J. A. (2014). Osteoarthritis incidence and trends in administrative health records from British Columbia, Canada. *Journal of Rheumatology*, *41*(6), 1147–1154. https://doi.org/10.3899/jrheum.131011

Rahman, W., Bauer, C. S., Bannister, K., Vonsy, J. L., Dolphin, A. C., & Dickenson, A. H. (2009). Descending serotonergic facilitation and the antinociceptive effects of pregabalin in a rat model of osteoarthritic pain. *Mol Pain*, *5*(45). https://doi.org/10.1186/1744-8069-5-45

Ratzlaff, C. R., Koehoorn, M., Cibere, J., & Kopec, J. A. (2012). Is lifelong knee joint force from work, home, and sport related to knee osteoarthritis? *International Journal of Rheumatology*, *2012*(1). https://doi.org/10.1155/2012/584193

Reichenbach, S., Rutjes, A., Nüesch, E., Trelle, S., & Jüni, P. (2010). Joint lavage for osteoarthritis of the knee (Review). *The Cochrane Database of Systematic Reviews*, (5). https://doi.org/10.1002/14651858.CD007320.pub2.www.cochranelibrary.com

Roberts, E., Delgado Nunes, V., Buckner, S., Latchem, S., Constanti, M., Miller, P., … Conaghan, P. G. (2016). Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Annals of the Rheumatic Diseases*, *75*, 552–559. https://doi.org/10.1136/annrheumdis-2014-206914

Roe, C. M., Mcnamara, A. M., & Motheral, B. R. (2002). Gender- and Age-Related Prescription Drug Use Patterns. *The Annals of Pharmacotherapy*, *36*, 30–39.

Rothnie, K. J., Müllerová, H., Thomas, S. L., Chandan, J. S., Smeeth, L., Hurst, J. R., … Quint, J. K. (2016). Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records. *Clinical Epidemiology*, *8*, 771–782. https://doi.org/10.2147/CLEP.S117867

Rudroju, N., Bansal, D., Talakokkula, S. T., Gudala, K., Hota, D., Bhansali, A., & Ghai, B. (2013). Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: a network meta-analysis. *Pain Physician*, *16*(6), E705-714. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24284851

Ryd, L., Brittberg, M., Eriksson, K., Jurvelin, J. S., Lindahl, A., Marlovits, S., … Zenobi-wong, M. (2015). Pre-Osteoarthritis: Definition and Diagnosis of an Elusive Clinical Entity. *Cartilage*, *6*(3), 156–165. https://doi.org/10.1177/1947603515586048

Salmon, J. H., Rat, A. C., Sellam, J., Michel, M., Eschard, J. P., Guillemin, F., … Fautrel, B. (2016). Economic impact of lower-limb osteoarthritis worldwide: a systematic review of cost-of-illness studies. *Osteoarthritis and Cartilage*, *24*(9), 1500–1508. https://doi.org/10.1016/j.joca.2016.03.012

Schifano, F. (2014). Misuse and abuse of pregabalin and gabapentin: Cause for concern? *CNS Drugs*, *28*(6), 491–496. https://doi.org/10.1007/s40263-014-0164-4

Schiphof, D., Boers, M., & Bierma-Zeinstra, S. M. A. (2008). Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. *Annals of the Rheumatic Diseases*, *67*(7), 1034–1036. https://doi.org/10.1136/ard.2007.079020

Schiphof, D., Oei, E. H. G., Hofman, A., Waarsing, J. H., Weinans, H., & Bierma-Zeinstra, S. M. A. (2014). Sensitivity and associations with pain and body weight of an MRI definition of knee osteoarthritis compared with radiographic Kellgren and Lawrence criteria: A population-based study in middle-aged females. *Osteoarthritis and Cartilage*, *22*(3), 440–446. https://doi.org/10.1016/j.joca.2013.12.017

Schwan, S., Sundström, A., Stjernberg, E., Hallberg, E., & Hallberg, P. (2010). A signal for an abuse liability for pregabalin-results from the Swedish spontaneous adverse drug reaction reporting system. *European Journal of Clinical Pharmacology*, *66*(9), 947–953. https://doi.org/10.1007/s00228-010-0853-y

Senderovich, H., & Jeyapragasan, G. (2018). Is there a role for combined use of gabapentin and pregabalin in pain control? Too good to be true? *Current Medical Research and Opinion*, *34*(4), 677–682. https://doi.org/https://doi.org/10.1080/03007995.2017.1391756

Shanthanna, H., Gilron, I., Rajarathinam, M., AlAmri, R., Kamath, S., Thabane, L., … Bhandari, M. (2017). Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. *PLoS Medicine*, *14*(8), 1–21. https://doi.org/10.1371/journal.pmed.1002369

Sharif, B., Kopec, J., Bansback, N., Rahman, M. M., Flanagan, W. M., Wong, H., … Anis, A. (2015). Projecting the direct cost burden of osteoarthritis in Canada using a microsimulation model. *Osteoarthritis and Cartilage*, *23*(10), 1654–1663. https://doi.org/10.1016/j.joca.2015.05.029

Siemieniuk, R. A. C., Harris, I. A., Agoritsas, T., Poolman, R. W., Brignardello-Petersen, R., Van de Velde, S., … Kristiansen, A. (2017). Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ (Clinical Research Ed.)*, *357*, j1982. https://doi.org/10.1136/BMJ.J1982

Silverwood, V., Blagojevic-Bucknall, M., Jinks, C., Jordan, J. L., Protheroe, J., & Jordan, K. P. (2015). Current evidence on risk factors for knee osteoarthritis in older adults: A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(4), 507–515. https://doi.org/10.1016/j.joca.2014.11.019

Smith, B., Higgins, C., Baldacchino, A., Kidd, B., & Bannister, J. (2012). Substance misuse of gabapentin. *British Journal of General Practice*, *62*(601), 406–407. https://doi.org/10.3399/bjgp12X653507

Smith, R. V, Havens, J. R., & Walsh, S. L. (2016). Gabapentin misuse, abuse, and diversion: A systematic review. *Addiction*, *111*(7), 1160–1174. https://doi.org/10.1016/S2215-0366(16)30284-X.Epidemiology

Sofat, N., Harrison, A., Russell, M., Ayis, S., Kiely, P. D., Baker, E. H., … Howe, F. (2017). The effect of pregabalin or duloxetine on arthritis pain: a clinical and mechanistic study in people with hand osteoarthritis. *Journal of Pain Research*, *10*, 2437–2449. https://doi.org/10.2147/JPR.S147640

Stahl, S. M., Porreca, F., Taylor, C. P., Cheung, R., Thorpe, A. J., & Clair, A. (2013). The diverse therapeutic actions of pregabalin: Is a single mechanism responsible for several pharmacological activities? *Trends in Pharmacological Sciences*, *34*(6), 332–339. https://doi.org/10.1016/j.tips.2013.04.001

Steel, N., Hardcastle, A. C., Bachmann, M. O., Richards, S. H., Mounce, L. T. A., Clark, A., … Campbell, J. (2014). Economic inequalities in burden of illness, diagnosis and treatment of five long-term conditions in England: panel study. *BMJ Open*, *4*(10), e005530. https://doi.org/10.1136/bmjopen-2014-005530

Steinman, M., Bero, L., Chren, M.-M., & Landefeld, C. (2006). Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents. *Annals of Internal Medicine*, (145), 284–293.

Tan, T., Barry, P., Reken, S., & Baker, M. (2010). Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. *BMJ*, *340*, c1079. https://doi.org/https://doi.org/10.1136/bmj.c1079

Thakur, M., Dickenson, A. H., & Baron, R. (2014). Osteoarthritis pain: nociceptive or neuropathic? *Nature Reviews. Rheumatology*, *10*(6), 374–80. https://doi.org/10.1038/nrrheum.2014.47

Thakur, M., Rahman, W., Hobbs, C., Dickenson, A. H., & Bennett, D. L. H. (2012). Characterisation of a peripheral neuropathic component of the rat monoiodoacetate model of osteoarthritis. *PLoS ONE*, *7*(3). https://doi.org/10.1371/journal.pone.0033730

The British Pain Society. (2012). *Use of medicines outside of their UK marketing authorisation in pain management and palliative medicine*. Retrieved from www.britishpainsociety.org

The Farr Institute. (2017). *Datasets that may be of interest to Primary Care Researchers in the UK*. Retrieved from http://www.farrinstitute.org/wp-content/uploads/2017/10/Datasets-that-may-be-of-interest-to-Primary-Care-Researchers-in-the-UK-May-2016.pdf

The International Neuromodulation Society. (2018). *How Has Neuromodulation Been Developed and Used?* Retrieved from http://www.neuromodulation.com/learn-more

The New York Times. (2009, September 2). Pfizer Pays $2.3 Billion to Settle Marketing Case. *Harris, G*. Retrieved from http://www.nytimes.com/2009/09/03/business/03health.html

Thiem, U., Lamsfuß, R., Günther, S., Schumacher, J., Bäker, C., Endres, H. G., … Pientka, L. (2013). Prevalence of Self-Reported Pain, Joint Complaints and Knee or Hip Complaints in Adults Aged ≥40 Years: A Cross-Sectional Survey in Herne, Germany. *PLoS ONE*, *8*(4), e60753. https://doi.org/10.1371/journal.pone.0060753

Thomas, E., Peat, G., & Croft, P. (2014). Defining and mapping the person with osteoarthritis for population studies and public health. *Rheumatology (United Kingdom)*, *53*(2), 338–345. https://doi.org/10.1093/rheumatology/ket346

Thomas, E., Wilkie, R., Peat, G., Hill, S., Dziedzic, K., & Croft, P. (2004). The North Staffordshire Osteoarthritis Project - NorStOP: prospective, 3-year study of the epidemiology and management of clinical osteoarthritis in a general population of older adults. *BMC Musculoskeletal Disorders*, *5*(2). https://doi.org/10.1186/1471-2474-5-2

Thompson, A., Ashcroft, D. M., Owens, L., van Staa, T. P., & Pirmohamed, M. (2017). Drug therapy for alcohol dependence in primary care in the UK: A Clinical Practice Research Datalink study. *PLOS ONE*, *12*(3), 1–14. https://doi.org/10.1371/journal.pone.0173272

Thorlund, J. B., Juhl, C. B., Roos, E. M., & Lohmander, L. S. (2015). Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ*, *350*, h2747. https://doi.org/10.1136/bmj.h2747

Treede, R. D., Jensen, T. S., Campbell, J. N., Cruccu, G., Dostrovsky, J. O., Griffin, J. W., … Serra, J. (2009). Neuropathic Pain: Redefinition and a Grading System for Clinical and Research Purposes. *Neurology*, *72*(14), 1282–1283. https://doi.org/10.1212/01.wnl.0000346325.50431.5f

Turkiewicz, A., De Verdier, M. G., Engström, G., Nilsson, P. M., Mellström, C., Stefan Lohmander, L., & Englund, M. (2015). Prevalence of knee pain and knee OA in southern Sweden and the proportion that seeks medical care. *Rheumatology (United Kingdom)*, *54*, 827–835. https://doi.org/10.1093/rheumatology/keu409

Turkiewicz, A., Neogi, T., Bjork, J., Peat, G., & Englund, M. (2016). All-cause Mortality in Knee and Hip Osteoarthritis and Rheumatoid Arthritis. *Epidemiology*, *27*(4), 479–485. https://doi.org/10.1097/EDE.0000000000000477

Turkiewicz, A., Petersson, I. F., Björk, J., Hawker, G., Dahlberg, L. E., Lohmander, L. S., & Englund, M. (2014). Current and future impact of osteoarthritis on health care: A population-based study with

projections to year 2032. *Osteoarthritis and Cartilage*, *22*(11), 1826–1832. https://doi.org/10.1016/j.joca.2014.07.015

U.S. Food & Drug Administration. (2018). Drugs@FDA: FDA Approved Drug Products. Retrieved March 23, 2018, from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

University of Manchester. (2018). Clinicalcodes.org. Retrieved February 20, 2018, from https://clinicalcodes.rss.mhs.man.ac.uk/

Valdes, A. M., Suokas, A. K., Doherty, S. A., Jenkins, W., & Doherty, M. (2014). History of knee surgery is associated with higher prevalence of neuropathic pain-like symptoms in patients with severe osteoarthritis of the knee. *Seminars in Arthritis and Rheumatism*, *43*(5), 588–592. https://doi.org/10.1016/j.semarthrit.2013.10.001

Van de Laar, M., Pergolizzi Jr., J. V, Mellinghoff, H. U., Merchante, I. M., Nalamachu, S., O'Brien, J., … Raffa, R. B. (2012). Pain treatment in arthritis-related pain: beyond NSAIDs. *The Open Rheumatology Journal*, *6*, 320–330. https://doi.org/10.2174/1874312901206010320

Van De Vijver, D. A. M. C., Walley, T., & Petri, H. (2004). Epidemiology of restless legs syndrome as diagnosed in UK primary care. *Sleep Medicine*, *5*(5), 435–440. https://doi.org/10.1016/j.sleep.2004.07.003

van Saase, J. L., van Romunde, L. K., Cats, A., Vandenbroucke, J. P., & Valkenburg, H. A. (1989). Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Annals of the Rheumatic Diseases*, *48*(4), 271–280. https://doi.org/10.1136/ard.48.4.271

Vedula, S. S., Bero, L., Scherer, R. W., & Dickersin, K. (2009). Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use. *New England Journal of Medicine*, *361*(20), 1963–1971. https://doi.org/10.1056/NEJMsa0906126

Verbeek, J., Mischke, C., Robinson, R., Ijaz, S., Kuijer, P., Kievit, A., … Neuvonen, K. (2017). Occupational Exposure to Knee Loading and the Risk of Osteoarthritis of the Knee: A Systematic Review and a Dose-Response Meta-Analysis. *Safety and Health at Work*, *8*(2), 130–142. https://doi.org/10.1016/j.shaw.2017.02.001

Vergne-salle, P. (2015). WHO Analgesic Ladder: Is It Appropriate for Joint Pain? From NSAIDS to Opioids. *International Association for the Study of Pain: Fact Sheet*, (18), 1–3.

Viñas-Bastart, M., Oms-Arias, M., Pedraza-Gutiérrez, À., Lizano-Díez, I., Modamio, P., & Mariño, E. L. (2017). Clinical Use of Pregabalin in General Practice in Catalonia, Spain: A Population-Based Cross-Sectional Study. *Pain Medicine*, *0*, 1–11. https://doi.org/10.1093/pm/pnx159

Vinik, A., Rosenstock, J., Sharma, U., Feins, K., Hsu, C., & Merante, D. (2014). Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. *Diabetes Care*, *37*(12), 3253–3261. https://doi.org/10.2337/dc14-1044

Visser, A. W., de Mutsert, R., le Cessie, S., den Heijer, M., Rosendaal, F. R., & Kloppenburg, M. (2015). The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Annals of the Rheumatic Diseases*, *74*(10), 1842–1847. https://doi.org/10.1136/annrheumdis-2013-205012

Vos, T., Allen, C., Arora, M., Barber, R. M., Brown, A., Carter, A., … Zuhlke, L. J. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and

injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1545–1602. https://doi.org/10.1016/S0140-6736(16)31678-6

Wallace, I. J., Worthington, S., Felson, D. T., Jurmain, R. D., Wren, K. T., Maijanen, H., … Lieberman, D. E. (2017). Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proceedings of the National Academy of Sciences*, 201703856. https://doi.org/10.1073/pnas.1703856114

Wallach, J. D., & Ross, J. S. (2018). Gabapentin Approvals, Off-Label Use, and Lessons for Postmarketing Evaluation Efforts, *319*(8), 776–778. https://doi.org/doi: 10.1001/jama.2017.21897

Walsh, D. (2016). Links between angiogenensis, inflammation and pain in OA. *Annals of the Rheumatic Diseases*, 18. https://doi.org/10.1136/annrheumdis-2016-eular.6377

Wang, H., Cheng, Y., Shao, D., Chen, J., Sang, Y., Gui, T., … Zha, Z. (2016). Metabolic Syndrome Increases the Risk for Knee Osteoarthritis: A Meta-Analysis. *Evidence-Based Complementary and Alternative Medicine*, *2016*. https://doi.org/10.1155/2016/7242478

Wang, Y. C., McPherson, K., Marsh, T., Gortmaker, S. L., & Brown, M. (2011). Health and economic burden of the projected obesity trends in the USA and the UK. *The Lancet*, *378*(9793), 815–825. https://doi.org/10.1016/S0140-6736(11)60814-3

Welsh Government. (2017). Prescriptions dispensed in the community. Retrieved January 9, 2018, from http://gov.wales/statistics-and-research/prescriptions-dispensed-community/?tab=previous&lang=en

Wiffen, P., Derry, S., Bell, R., Rice, A., Tolle, T., Phillips, T., & Moore, R. (2017). Gabapentin for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews*, (6). https://doi.org/10.1002/14651858.CD007938

Williams, T., Van Staa, T., Puri, S., & Eaton, S. (2012). Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. *Therapeutic Advances in Drug Safety*, *3*(2), 89–99. https://doi.org/10.1177/2042098611435911

Wills, A. K., Black, S., Cooper, R., Coppack, R. J., Hardy, R., Martin, K. R., … Kuh, D. (2012). Life course body mass index and risk of knee osteoarthritis at the age of 53 years: evidence from the 1946 British birth cohort study. *Annals of the Rheumatic Diseases*, *71*(5), 655–660. https://doi.org/10.1136/ard.2011.154021

Windfuhr, K., While, D., Kapur, N., Ashcroft, D. M., Kontopantelis, E., Carr, M. J., … Webb, R. T. (2016). Suicide risk linked with clinical consultation frequency, psychiatric diagnoses and psychotropic medication prescribing in a national study of primary-care patients. *Psychological Medicine*, *46*(16), 3407–3417. https://doi.org/10.1017/S0033291716001823

Wing, K., Bhaskaran, K., Smeeth, L., van Staa, T. P., Klungel, O. H., Reynolds, R. F., & Douglas, I. (2016). Optimising case detection within UK electronic health records: use of multiple linked databases for detecting liver injury. *BMJ Open*, *6*, e012102. https://doi.org/10.1136/bmjopen-2016-012102

Wright, A., Moss, P., Benson, H., Will, R., & Chowalloor, P. (2017). SAT0487 A randomized, blinded, comparator-controlled trial investigating a 4-week course of lyrica in subjects with knee osteoarthritis who exhibit neuropathic pain, compared with a 4-week course of paracetamol. *Annals of the Rheumatic Diseases*, *76*, 960. https://doi.org/10.1136/annrheumdis-2017-eular.5656

Yu, D., Jordan, K. P., Bedson, J., Englund, M., Blyth, F., Turkiewicz, A., … Peat, G. (2017). Population trends in the incidence and initial management of osteoarthritis: age-period-cohort analysis of the

Clinical Practice Research Datalink, 1992–2013. *Rheumatology*, *56*(11), 1902–1917. https://doi.org/10.1093/rheumatology/kex270

Yu, D., Jordan, K., & Peat, G. (2018). Underrecording of osteoarthritis in United Kingdom primary care electronic health record data. *Clinical Epidemiology*, *10*, 1195–1201.

Yu, D., Peat, G., Bedson, J., & Jordan, K. P. (2015). Annual consultation incidence of osteoarthritis estimated from population-based health care data in England. *Rheumatology (United Kingdom)*, *54*(11), 2051–2060. https://doi.org/10.1093/rheumatology/kev231

Zaccara, G., Giovannelli, F., Giorgi, F. S., Franco, V., Gasparini, S., & Benedetto, U. (2017). Tolerability of new antiepileptic drugs: a network meta-analysis. *European Journal of Clinical Pharmacology*, *73*(7), 811–817. https://doi.org/10.1007/s00228-017-2245-z

Zeggini, E., Panoutsopoulou, K., Southam, L., Rayner, N. W., Day-Williams, A. G., Lopes, M. C., … Loughlin, J. (2012). Identification of new susceptibility loci for osteoarthritis (arcOGEN): A genome-wide association study. *The Lancet*, *380*(9844), 815–823. https://doi.org/10.1016/S0140-6736(12)60681-3

Zghebi, S. S., Steinke, D. T., Carr, M. J., Rutter, M. K., Emsley, R. A., & Ashcroft, D. M. (2017). Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. *Diabetes, Obesity and Metabolism*, *19*(11), 1537–1545. https://doi.org/10.1111/dom.12964

Zhong, V. W., Juhaeri, J., Cole, S. R., Shay, C. M., Gordon-Larsen, P., Kontopantelis, E., & Mayer-Davis, E. J. (2018). HbA1C variability and hypoglycemia hospitalization in adults with type 1 and type 2 diabetes: A nested case-control study. *Journal of Diabetes and Its Complications*, *32*(2), 203–209. https://doi.org/10.1016/j.jdiacomp.2017.10.008

8 Appendices

Appendix 1 Study Protocol and Related Materials

Appendix 1.1 Study Protocol submitted to Independent Scientific Advisory Committee (ISAC).

Approved April 2018

ISAC APPLICATION FORM

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***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)*

Gabapentinoid drug prescriptions in patients with osteoarthritis: an analysis of data from the Clinical Practice Research Datalink.

[§]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 X

**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 X

**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 :*

This protocol underwent independent scientific peer review by two senior researchers based within the Institute for Primary Care & Health Sciences at Keele University. As a result of the feedback, aspects of the design and analysis were modified and some sections revised for clarity.

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	x	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:

- Gabapentinoid prescriptions among adults with osteoarthritis
-
-
-

[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	x	Presentation at scientific conference	x
Presentation at company/institutional meetings	x	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.

GEORGE PEAT, Professor of Clinical Epidemiology, Keele University, g.m.peat@keele.ac.uk

§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	x **CV number:** 280_15S
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)

ARTHRITIS RESEARCH UK PRIMARY CARE CENTRE, RESEARCH INSTITUTE FOR PRIMARY CARE & HEALTH SCIENCES, KEELE UNIVERSITY, KEELE, STAFFORDSHIRE ST5 5BG

9. Corresponding Applicant§

Please state the full name, affiliation(s) and e-mail address below:

§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	X
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: THOMAS APPLEYARD

CV has been previously submitted to ISAC	☐ **CV number:**
A new CV is being submitted with this protocol	x
An updated CV is being submitted with this protocol	☐

Other investigator: DAHAI YU

CV has been previously submitted to ISAC	x **CV number:** 282_15S
A new CV is being submitted with this protocol	☐
An updated CV is being submitted with this protocol	☐

Other investigator: JOHN BEDSON

CV has been previously submitted to ISAC	☐ **CV number:**
A new CV is being submitted with this protocol	X

An updated CV is being submitted with this protocol ☐

Other investigator: JULIE ASHWORTH
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol **X**
An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary]

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

The authors have no conflicts of interest to declare

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

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	**x**	**x**

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)* YU	X	☐
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)* YU	X	☐
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)* BEDSON	X	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

1. Blågestad T, Nordhus IH, Grønli J, Engesæterf LB, Ruths S, Ranhoff AH, et al. Prescription trajectories and effect of total hip arthroplasty on the use of analgesics, hypnotics, antidepressants, and anxiolytics: results from a population of total hip arthroplasty patients. Pain. 2016 Mar;157(3):643–51.
2. Cartagena, F. J., Porter, L., McManus, S., Strang, J., Hickman, M., Reed, K., & Smith, N. (2017). *Prescribing patterns in dependence forming medicines.* Available at: http://phrc.lshtm.ac.uk/papers/PHRC_014_Final_Report.pdf Last accessed: 13 Nov 2017
3. Soni A, Batra RN, Gwilym SE, Spector TD, Hart DJ, Arden NK, Cooper C, Tracey I, Javaid MK. Neuropathic features of joint pain: a community-based study. Arthritis Rheum. 2013 Jul;65(7):1942-9. doi: 10.1002/art.37962.

SECTION C: ACCESS TO THE DATA

14. 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	X	*Please specify name and country:* KEELE UNIVERSITY, UK
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	X	*Please specify name and country:* KEELE UNIVERSITY
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:*

16. 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**	X
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

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies	X	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

18. Does this protocol seek access to linked data

Yes* **x** 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 and the Pregnancy Register **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 Reference number (where available) Date of contact

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.

19. Please select the source(s) of linked data being requested[8]

[8]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
☐ MINAP (Myocardial Ischaemia National Audit Project)
☐ Cancer Registration Data*
☐ PROMS (Patient Reported Outcomes Measure)**
☐ CPRD Mother Baby Link
☐ Pregnancy Register

☐ Practice Level Index of Multiple Deprivation (Standard)
☐ Practice Level Index of Multiple Deprivation (Bespoke)
X Patient Level Index of Multiple Deprivation***
☐ Patient Level Townsend Score ***
☐ Other**** *Please specify:*

**Applicants seeking access to cancer registration 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

20. 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* ***<u>not</u>*** *be included in this count)* **1 (CPRD GOLD)**

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

21. Is linkage to a <u>local</u>[¥] dataset with <1 million patients being requested?

Yes* ☐ No **X**

**If yes, please provide further details:*
[¥] Data from defined geographical areas i.e. non-national datasets.

22. 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 **X**

** If yes, please provide further details:*

23. 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 **X**

SECTION E: VALIDATION/VERIFICATION

24. Does this protocol describe a purely observational study using CPRD data?

Yes* **X** 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.*

25. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No **X**

** 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.*

26. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No **X**

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

27. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No **X**

** Please state what will be collected:*

SECTION F: DECLARATION

28. 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: GEORGE PEAT Date: 27 November 2017 e-Signature (type name): George PEAT

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Prescriptions for gabapentinoid drugs in patients with osteoarthritis: an analysis of data from the Clinical Practice Research Datalink.

B. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Osteoarthritis (OA) is a large and growing problem. Doctors may have started to prescribe medications ('gabapentinoids') traditionally used for epilepsy and neuropathic pain (nerve pain) to control osteoarthritis pain. This could be due to the ineffectiveness of existing painkillers and to research suggesting that osteoarthritis pain can sometimes be partly 'neuropathic'. Yet there is very limited evidence of the effectiveness of gabapentinoids in this population and mounting concern over the increasing use of these medications in general because of their addictive properties and potential for illegal misuse.

Our study will investigate recent UK trends in the prescribing of gabapentinoids in patients with OA to address the following questions:

- How many patients with OA are prescribed a gabapentinoid, and has their use changed over time?
- Does this prescribing vary by a patient's age, gender or what region they live in?
- How much of this prescribing might be for OA, rather than for other conditions a patient may have?
- How often is a gabapentinoid prescribed alongside an opioid, another potentially addictive group of medications?
- How does gabapentinoid prescribing vary when a patient has a knee replacement?

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

In the context of concern over the growing rate of gabapentinoid prescriptions and their potential for diversion and misuse, anecdotal evidence of the prescription for osteoarthritis - a highly common painful condition but in which there is little evidence of their effectiveness - warrants further investigation.
Our prospective cohort study will follow patients from new diagnosis of OA in 1995-2015 to estimate the proportion prescribed a gabapentinoid, the trend in this over time, overall and stratified by age, sex, area-level deprivation and geographical region. The proportion with co-prescription of opioid analgesic will be described. To estimate what proportion of these gabapentinoid prescriptions might be attributable to osteoarthritis we will exclude prescriptions in those with a licensed indication (e.g. epilepsy, neuropathic pain). Sensitivity analyses will explore the effect of widening the time period around gabapentinoid prescription during which a licensed indication is recorded. In a final before-after study we will explore rates of

gabapentinoid prescription before and after total knee arthroplasty.

D. Objectives, Specific Aims and Rationale

Rationale: Prescriptions for gabapentinoids have increased markedly over recent years and pain appears the main reason. It is unclear whether the increasing use of these drugs for osteoarthritis has contributed to this overall rise. New evidence on their pattern of use could help inform clinical practice guidelines for OA.

The overall aim of this study is to describe recent trends and patterns in the prescription of gabapentinoids in patients with osteoarthritis presenting to UK general practice.

Specific objectives:

1. To estimate the incidence rate of (any) recorded prescriptions of gabapentinoids in patients newly diagnosed with osteoarthritis in 1995-2015
2. To explore the variation in gabapentinoid prescription in patients with osteoarthritis by age, sex, calendar year, geographical region, and area-level deprivation
3. To estimate the proportion of gabapentinoid prescriptions in patients with osteoarthritis that are attributable to a licensed comorbid indication
4. To explore the frequency of gabapentinoid and opioid co-prescription in patients with osteoarthritis
5. To compare the rate of gabapentinoid prescription before and after primary total knee replacement and compare this with the pattern for prescribed NSAIDs and opioid analgesics

E. Study Background

Osteoarthritis is a significant and growing problem for population health globally.[1] National data for England suggest that between 800,000 and 1 million patients consult general practice each year for osteoarthritis.[2]

Amid concerns over adverse effects and lack of efficacy of current pharmacological treatments, such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics,[3-5] there is anecdotal evidence that several other classes of drug, including gabapentinoids (e.g. Gabapentin and Pregabalin). are being used for pain control in osteoarthritis. These drugs have been licensed for use in epilepsy and neuropathic pain but a recent rapid analysis of CPRD data has confirmed a pattern of long-term increases in the prescribing of these drugs since the turn of the century in UK.[6] Gabapentinoids are regarded as dependence-forming medicines and have attracted increasing concern amid official figures in England & Wales showing an increase in the numbers of deaths linked to these drugs.[7] In 2014, advice for prescribers was issued by Public Health England and NHS England.[8] However, prescribing and reports of harm have continued to increase.[9,10] Therefore in September 2017 the UK government accepted recommendations from the Advisory Council on the Misuse of Drugs[11] that gabapentin and pregabalin should be controlled as class C substances under the Misuse of Drugs Act 1971.[12,13]

The increase in prescribing has been attributed to their use for pain ("probably due to their use for pain"[13]). This is assumed to refer to the neuropathic pains that gabapentinoids are licensed for, although clear evidence of this is difficult to obtain. An analysis of THIN data reported that the proportion of pregabalin prescriptions between 2005-2009 that were attributed to epilepsy, neuropathic pain, generalised anxiety disorder and 'other' diagnoses was 4.2%, 18.3%, 21.6, and 61.1% respectively although this was highly sensitive to the code lists and time window used[14](see Section S. below). No evaluation of the trend in use was

reported in that study. Even if neuropathic pain has been the indication showing the highest growth in gabapentinoid prescriptions, it is important to recognise that the list of conditions in which a 'neuropathic pain component' is claimed has been expanding over this time. Osteoarthritis is one of these with the claim of a neuropathic pain component based predominantly on findings from pre-clinical models (monosodium idioacetate OA rat model) descriptions of neuropathic-like symptoms and signs in qualitative and cohort studies.[15-18] To date there are three small (n<100) RCTs of gabapentinoids for osteoarthritis pain. Studies describing patterns of prescription analgesia use in primary care,[19-21] and specifically in patients with osteoarthritis,[22] have tended to focus on opioid analgesia and have not yet considered these drugs.

Given the very high numbers of patients with osteoarthritis, even the prescription of gabapentinoids to a relatively small proportion of cases would represent quite large absolute numbers. Furthermore, opioid prescriptions are already common, and rising, for osteoarthritis and the co-prescribing of two dependence-forming classes of medicines - gabapentinoids and opioids - in patients with osteoarthritis is a particular concern. Finally, osteoarthritis provides a potential 'natural experiment' for evaluating dependence on medicines. Primary total hip and knee replacement are highly effective in relieving pain in end-stage osteoarthritis. Using joint replacement registry data linked to prescriptions databases in Norway, Blagestad and colleagues[23] recently evaluated the change in frequency of different analgesics and antidepressant medicines before and after joint replacement. We intend to extend their work by including gabapentinoid prescription.

F. Study Type

Descriptive study

G. Study Design

(i) Prospective cohort study (objectives 1-4)
Incident consulting cases of OA identified between 1995-2015 will be followed from index consultation to first censoring event (see K. below). The incidence rate of gabapentinoid prescription will be estimated within these fixed cohorts.

(ii) Longitudinal before-after study (objective 5)
Among patients with a Read-coded consultation for clinical OA and identified as having undergone a primary total knee replacement between 1 January 2003 and 31 December 2015, the proportion of patients with a recorded gabapentinoid prescription in each 6-month time window from 3 years pre- to 1 year post-arthroplasty will be estimated.

H. Feasibility counts

(i) From our previous CPRD analysis (ISAC 14_090), we identified 371,782 incident cases of diagnosed OA between 2000-2013 (minimum number of incident cases in any calendar year during this time is just over 14,000). The corresponding figure for the broader case definition of 'clinical OA' is approximately 3-4 times this.

(ii) From our previous CPRD analysis (ISAC 15_211), among 133,600 OA patients undergoing a primary total knee replacement 2.9% of these patients had at least one prescription of gabapentin or pregabalin in the 3 years prior to TKR.

I. Sample size considerations

Given an expected maximum cumulative incidence proportion of 0.05, desired width of confidence interval of 0.01, and 95% confidence level, a minimum cohort sample size of 7,299 incidence OA cases would be needed. This is comfortably below the smallest number of incident OA cases per year identified from the feasibility counts although estimates from stratified analyses (e.g. by geographical region or IMD quintile) will have lower precision.

J. Data Linkage Required (if applicable):§

§Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy

None.

K. Study population

(i) Incident cases of diagnosed OA, aged 40 years and over, consulting UK general practice between 1995-2015 will be identified *[objectives 1-4]*

For each patient, the entry date into the cohort will be the date of first osteoarthritis consultation. Five criteria should be met by the entry date: 1) age 40 years or over on date of osteoarthritis consultation; 2) at least three years prior registration; 3) the data of registered practice is deemed to be of research quality in prior three years; 4) no previous recorded knee or hip replacement in the prior 3 years before the entry date; (5) no gabapentinoid prescription in the prior 3 years before the entry date.

For each patient, we will also determine an exit date, which is the earliest of the following dates: date of first gabapentinoid prescription (following OA diagnosis), date of recorded knee or hip replacement, date of death, date of deregistration with practice, date of last collection of practice data, or the study end date (31 December 2016).

We will apply the same code list and methods for 'incident diagnosed OA' as in our previous CPRD analysis (ISAC 14_090)[22] (*Appendix 1*). In sensitivity analyses we will repeat the analyses using a broader definition of 'incident clinical OA', again using codelists and methods from ISAC 14_090 (*Appendix 2*).

The reason for including incident OA cases from 1995 (i.e. several years before gabapentinoids were licensed for neuropathic pain) is that gabapentinoids may be used for OA many years after the diagnosis of OA is first recorded.

(ii) Patients aged 40 years and over who have undergone primary total knee replacement, 2003-2015 *[objective 5]*
As per (i) above, the following additional criteria should be met: (1) at least 3 years prior registration and one year post-replacement registration; (2) practice data is deemed up to standard for the 4-year period.

Primary total knee replacement cases will be identified using the same code list previously developed[24] and applied[22] in CPRD (ISAC 15_211) (*Appendix 3*)

L. Selection of comparison group(s) or controls

N/A

M. Exposures, Health Outcomes§ and Covariates

§Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy

Health outcome = recorded prescription of gabapentinoids (code lists derived from[6]) (*Appendix 4*)

Covariates: age; sex; ethnicity; calendar year; geographical region; IMD 2010 decile/quintile; main licensed indications for gabapentinoids - epilepsy, neuropathic pain, and generalised anxiety disorder (code lists provided in *Appendix 5*); recorded prescription of opioid analgesic (as per previous protocol (Protocol Reference_NCQ10623 13_135RAMnA *(Appendix 6)*); multimorbidity (Charlson Comorbidity Index)

N. Data/ Statistical Analysis

(i) Objectives 1 & 2. Simple descriptive statistics will be used to summarise the frequency of recorded gabapentinoid prescriptions in OA cohort members. Within OA cohort members with gabapentinoid prescription during follow-up, the type and pattern of gabapentinoid prescription will be described. Lexis expansion will be used to explore age- and calendar period-specific incidence rates of (first) recorded gabapentinoid prescription in incident OA cohort members. Age-gender standardised incidence rates of recorded gabapentinoid prescription in each incident OA cohort will be estimated with using 2015 English population as the standard population; the age-gender standardised incidence rates will also be estimated by geographical region and IMD quintile. Survival analysis will be used to observe the time to first prescription in each OA cohort by overall, gender, age stratum, geographical region, and IMD quintile. Multivariable Cox regression analyses will be used to explore the association between incident prescription of gabapentinoid and age, sex, calendar year, geographical region, multimorbidity and IMD quintile, stratified by year of incident OA diagnosis and with baseline as 2002 (year that gabapentin was licensed for neuropathic pain). Multilevel mixed effect models will be used to estimate the overall above associations across OA cohorts defined by calendar year of incident OA consultation.

Objective 3. We will exclude individuals with any diagnostic code for epilepsy, neuropathic pain, or GAD in the 3 years prior to baseline and re-estimate incidence rates. In the whole incident OA cohort, we will also use simple descriptive statistics to explore the proportion of gabapentinoid prescriptions that have a recorded diagnosis of epilepsy, neuropathic pain or GAD within 14 days prior and 90 days after the prescription. Any time trend in the proportion of gabapentinoid prescriptions with a 'licensed indication code' over time will be explored by stratifying by year of gabapentinoid prescription.

Objective 4. Simple descriptive statistics will be used to describe the proportion of OA cohort members with a gabapentinoid prescription who also have received one or more prescription for opioid analgesic within a 28-day period of their gabapentinoid prescription. Any time trend in the proportion with opioid co-prescription will be explored by stratifying by year of gabapentinoid prescription.

(ii) Objective 5. Simple descriptive statistics will be used to describe the proportion of patients with a gabapentinoid prescription in 6-month intervals covering the period 1 year prior to, and 1 year following, primary total knee replacement. For comparative purposes we will perform the same analysis in the same patient group for opioid prescription.

O. Plan for addressing confounding

Confounding, in this descriptive study, relates mainly to the confidence in attributing a gabapentinoid prescription to a given diagnosis (whether osteoarthritis or to one of the licensed comorbid indications such as epilepsy). Following on from our previous work in CPRD and the analyses of Asomaning[14] we anticipate many instances where a prescription of gabapentinoid cannot be clearly linked to a diagnostic code within a short interval (e.g. -14 days to +90 days). We plan to address this in a number of different ways. In sensitivity analyses we will explore expanding this time window to the extreme of the entire duration of a patient's

follow up (between initial OA consultation and gabapentinoid prescription), plus the three year period prior to their OA diagnosis. Gabapentinoid prescriptions in patients with at least one licensed comorbid indication Read code over this extended period will be interpreted as potentially attributable to a licensed comorbid indication.

In both analyses (i) and (ii) the risk of confounding by calendar time will be handled by stratification (where numbers permit) or multivariable adjustment.

P. Plans for addressing missing data

Of the variables we intend to use, ethnicity is likely to have important levels of missing data which we will handle by a 'missing' category for this covariate.

Q. Patient or user group involvement (if applicable)

We have not involved PPIE in the design of this study but we would seek to present our findings to a mixed audience including members of our Institute's Research User Group for comment and feedback.

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

We intend to submit the results of this study for presentation at regional (Midlands RCGP), national (Society for Academic Primary Care, British Society for Rheumatology) and international (Osteoarthritis Research Society International) annual scientific meetings. We will target a general medical or specialist audience for publication in open-access peer-reviewed journals (e.g. BMJ, Annals of the Rheumatic Diseases, Osteoarthritis & Cartilage). In reporting the results of this study, we will follow the STROBE[25], RECORD[26] and good pharmacoepidemiology practice[27] guidelines on the reporting of observational studies and those using routinely collected healthcare data. As Arthritis Research UK's Centre of Excellence for Primary Care our research group has close links with the charity's policy and public health strategy unit and we will seek to disseminate our findings more broadly through this channel.

S. Limitations of the study design, data sources, and analytic methods

The confidence with which attribution of gabapentinoid prescription in patients with OA can be made to their OA or to other licensed comorbid indications within this population of interest is expected to be sensitive to (a) the diagnostic code list used to define osteoarthritis and the licensed indications (epilepsy, neuropathic pain, generalised anxiety disorder), and (b) the length of the time window before and after gabapentinoid prescription within which a relevant diagnostic code is searched to identify a case of OA or licensed indication. For example, Asomaning et al.[14] analysing THIN data found that the proportion of pregabalin prescriptions attributed to neuropathic pain diagnoses rose from 18.3% to 97.8% when an expanded code list was used and the time window was expanded to any time prior to prescription + up the 6 months post-prescription (-12 to +6 months for any back pain code). Our plans to handle this as described in Section O. above.

A sensitivity analysis is planned to evaluate the effect of OA case definition on the findings. Our primary analysis is based on diagnosed OA, i.e. N05 Read codes. Although they are likely to have a lower PPV, non-specific symptom codes for OA, e.g. arthralgia are often used by GPs when managing OA.

Small cell numbers of gabapentinoid prescriptions are expected when stratifying time pre- and post-replacement into 6-month intervals. No cell with fewer than 5 events will be reported as per ISAC governance

guidance.

T. References

1. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388:1603–58.
2. Arthritis Research UK. Osteoarthritis in General Practice: Data and Perspectives. Chesterfield, UK: Arthritis Research UK; 2013.
3. Doherty M, Hawkey C, Goulder M, *et al.* A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. *Ann Rheum Dis* 2011;70:1534–41.
4. Roberts E, Delgado Nunes V, Buckner S, *et al.* Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* 2016;75(3):552-9.
5. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, Trelle S. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis.Lancet. 2017 Jul 8;390(10090):e21-e33.
6. Cartagena Farias J, Porter L, McManus S, Strang J, Hickman M, Reed K, Smith N. Prescribing patterns in dependence forming medicines. London: NatCen. 2017. Available at: http://phrc.lshtm.ac.uk/papers/PHRC_014_Final_Report.pdf Last accessed: 14 Nov 2017.
7. ONS. Deaths related to drug poisoning in England and Wales: 2016 registrations. Aug 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations#people-aged-40-to-49-years-have-the-highest-rate-of-drug-misuse-deaths Last accessed: 14 Nov 2017.
8. Public Health England. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin, Dec 2014. Available at: https://www.gov.uk/government/publications/pregabalin-and-gabapentin-advice-for-prescribers-on-the-risk-of-misuse Last accessed: 14 Nov 2017.
9. OpenPrescribing beta. Available at: https://openprescribing.net/ Last accessed: 29 Mar 2018.
10. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs. 2017 Mar;77(4):403-426. doi: 10.1007/s40265-017-0700-x.
11. Advisory Council on the Misuse of Drugs. Diversion and Illicit Supply of Medicines. Dec 2016. Available at: https://www.gov.uk/government/publications/diversion-illicit-supply-of-medicines Last accessed: 14 Nov 2017.
12. Iacobucci G. UK government to reclassify pregabalin and gabapentin after rise in deaths. BMJ 2017;358:j4441
13. Chaplin S. Trends in primary care prescribing, 2004-2014. Prescriber 2015, Oct 5, 14-18. Available at: http://www.prescriber.co.uk/year-volume-issues/5oct2015/ Last accessed: 14 Nov 2017.
14. Asomaning, K. et al. (2016) 'Pregabalin prescriptions in the United Kingdom: a drug utilisation study of the THIN primary care database'. International Journal of Clinical Practice, vol. 70(5) pp 380-388. http://dx.doi.org/10.1111/ijcp.12791
15. Hochman JR, Gagliese L, Davis AM, Hawker GA. (2011). Neuropathic pain symptoms in a community knee OA cohort. *Osteoarthritis and Cartilage, 19*(6), 647–654. https://doi.org/10.1016/j.joca.2011.03.007
16. Ohtori S, Orita S, Yamashita M, Ishikawa T, Ito T, Shigemura T, et al. Existence of a neuropathic pain component in patients with osteoarthritis of the knee.Yonsei Med J. 2012 Jul 1;53(4):801-5. doi: 10.3349/ymj.2012.53.4.801.
17. Soni A, Batra RN, Gwilym SE, Spector TD, Hart DJ, Arden NK, et al. Neuropathic features of joint pain: a community-based study. Arthritis Rheum. 2013 Jul;65(7):1942-9. doi: 10.1002/art.37962.
18. Dimitroulas T, Duarte RV, Behura A, Kitas GD, Raphael JH. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. Semin Arthritis Rheum. 2014 Oct;44(2):145-54.
19. Bedson J, Belcher J, Martino OI, Ndlovu M, Rathod T, Walters K, Dunn KM, Jordan KP. The effectiveness of national guidance in changing analgesic prescribing in primary care from 2002 to 2009: an observational database study. Eur J Pain. 2013 Mar;17(3):434-43.
20. Ndlovu M, Bedson J, Jones PW, Jordan KP. Pain medication management of musculoskeletal conditions at first presentation in primary care: analysis of routinely collected medical record data. BMC Musculoskelet Disord. 2014 Dec 10;15:418
21. Bedson J, Chen Y, Hayward RA, Ashworth J, Walters K, Dunn KM, Jordan KP. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. Pain. 2016 Jul;157(7):1525-31.
22. Yu D, Jordan KP, Bedson J, Englund M, Blyth F, Turkiewicz A, Prieto-Alhambra D, Peat G. Population trends in the incidence and initial management of osteoarthritis: age-period-cohort analysis of the Clinical Practice Research Datalink, 1992-2013. Rheumatology (Oxford). 2017 Nov 1;56(11):1902-1917.
23. Blågestad T, Nordhus IH, Grønli J, Engesæter LB, Ruths S, Ranhoff AH, Bjorvatn B, Pallesen S.Prescription trajectories and effect of total hip arthroplasty on the use of analgesics, hypnotics, antidepressants, and anxiolytics: results from a population of total hip arthroplasty patients.Pain. 2016 Mar;157(3):643-51.
24. Culliford DJ, Maskell J, Beard DJ, Murray DW, Price AJ, Arden NK. Temporal trends in hip and knee replacement in the

United Kingdom: 1991 to 2006. J Bone Joint Surg Br. 2010 Jan;92(1):130-5.
25. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007 Oct 16;4(10):e296.
26. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM; RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015 Oct 6;12(10):e1001885.
27. Public Policy Committee, International Society of Pharmacoepidemiology.Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):2-10.

List of Appendices *(Submit all appendices as separate documents to this application)*

Appendix 1. Code lists for diagnosed osteoarthritis
Appendix 2. Code lists for clinical osteoarthritis
Appendix 3. Code lists for primary total knee replacement
Appendix 4. Code lists for gabapentinoids
Appendix 5. Code lists for potential other indications for gabapentinoids
Appendix 6. Code lists for opioids

Appendix 1.2 Linkage Form submitted to the ISAC Secretariat for use of Index of Multiple Deprivation Data (not included in this thesis)

Medicines & Healthcare products Regulatory Agency

CPRD More Dimensions to Data

LINKAGE REQUEST FORM

Please complete the form below and email this together with your list of patient ids, **including** each patient's linkage eligibility flag/s (e.g. hes_e=1, death_e=1 etc) in text file format (.txt) to enquiries@cprd.com. Please ensure that the Chief Investigator of this protocol is copied in on the request email to CPRD Enquiries. As the provision of ALL linked data is subject to ISAC approval, please check that you have the necessary approvals to request these data. **Please refer to the superscript footnotes for additional information.**
N.B. Please ensure a Third Party Agreement (TPA) has been arranged (if required) between the licence holding institution and third party collaborator (this should include **all investigators** who will handle the raw data) before submitting this linkage request form.
Linked data will be supplied **within 10 working days** of receipt of a correctly completed request form, acceptable patient ID file and respective TPAs.

Requestor Name: Professor George Peat	**Organisation:** Keele University	
Requestor Email Address: g.m.peat@keele.ac.uk	**Requestor Telephone No:** 01782 733906	
Protocol No: 18_007	**Date of ISAC approval:** 05/04/18	**Date of Request:** 19/04/18
Study Title: Gabapentinoid drug prescriptions in patients with osteoarthritis: an analysis of data from the Clinical Practice Research Datalink.		
GOLD Database used in your extraction December 2017	**Linkage Eligibility Set**[§] Set 15	**Number of patients in your patient list:** 383,680
Third Party Agreement (TPA)[†] Copies of all signed relevant TPA(s) must be provided if the Organisation completing this Linkage Request Form, or any third-party person or organisation whatsoever who will be handling CPRD GOLD data or Linked Data on behalf of the Organisation, is not party as a 'Licensee' to a current and valid CPRD GOLD Database licence agreement ☐ TPA(s) included **x** Current GOLD Database Licensee please give details: Our CPRD GOLD license expired on 8 March 2018. We had submitted our ISAC proposal in December 2017, hoping to complete the approval process and obtain IMD linkage before the license expired. Unfortunately our response to a request to include complete CVs that we submitted on 8 Jan 2018 was not picked up for several weeks. As a result our ISAC proposal was not approved until 5 Apr 2018. Given the unfortunate delays, I hope it will still be possible to obtain the linkage needed for this study. I'm aware that for a similar situation (CPRD00021942 Data Linkage Request RE: 21769; CI: Ross Wilkie) the linked data were released through an arrangement with Nick Liptrot for a one-time dataset agreement reflecting the new CPRD terms and perhaps that would be the mechanism here?		
Please select the linked data requested below [§]	**Please provide justification for requesting each linked data resource below** *(e.g. covariate, denominator data derivation, case identification, study outcome)*	
☐ Integrated HES ☐ Basic HES[‡] ☐ Full HES[‡]		
☐ HES Outpatient[‡]		

☐ HES A&E‡	
☐ HES DID‡	
☐ HES Patient Reported Outcomes Measures (HES PROMs)	
☐ Mental Health Data#	
☐ ONS Mortality Data	
CPRD Practice Level Deprivation Data¥ ☐ Standard (Most up-to-date) ☐ Bespoke *(please refer to the practice postcode linkage documentation)*	
Patient Level Deprivation Data*¥ ☐ IMD2004 ☐ IMD2007 ☐ IMD2010 **x** IMD2015 ☐ Townsend	The use of the IMD2015 DECILE score in our analyses will be as a covariate, to assess the relationship between socioeconomic deprivation and rate of gabapentinoid prescribing in the OA population. Socioeconomic deprivation has been found by other studies to be associated with an increased rate of opioid prescribing, another class of dependence-forming medications.[1]
Please note that all data will be provided via secure FTP	

1 Foy R, Leaman B, McCrorie C, *et al* Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics *BMJ Open* 2016;**6:**e010276. doi: 10.1136/bmjopen-2015-010276

§ The source file used to identify patients eligible for linkage to CPRD GOLD and one or more linked data source(s).
ß Subject to ISAC approval.
† Relevant TPA(s) are defined solely as the CPRD-approved 'Annex B: Contractor Letter' fully-executed by the third party Organisation and the GOLD Database Licensee. Copies of all signed TPA(s) must be submitted with this form. CPRD will not be able to process this form or deliver any data request without all relevant TPA(s).
‡ Access associated with data charges except for annual licence holders of these data.
# Mental Health Data set is only available from **Linkage Set 14**
* Patient level Index of Multiple Deprivation (IMD) data will only be supplied for a single evaluation year (2004 OR 2007 OR 2010 OR 2015); Townsend data cannot be supplied together with IMD patient level data.
¥Users **should** specify whether data is required to be stratified by quintiles, deciles or twentiles. **NB**: CPRD Practice Level Deprivation Data can only be stratified by quintiles or deciles.

Appendix 2 Read Codes used in CPRD analysis

Appendix 2.1 Read Codes of Diagnostic Osteoarthritis

Read Code	Read term
N05..11	Osteoarthritis
N05z211	Elbow osteoarthritis NOS
N05z400	Osteoarthritis NOS, of the hand
N05z611	Knee osteoarthritis NOS
N053512	Hip osteoarthitis NOS
N053611	Patellofemoral osteoarthritis
N05z712	Foot osteoarthritis NOS
N05z.11	Joint degeneration
N05z412	Thumb osteoarthritis NOS
N05z511	Hip osteoarthritis NOS
N05zB00	Osteoarthritis NOS, of acromioclavicular joint
N05zL00	Osteoarthritis NOS, of knee
N05..00	Osteoarthritis and allied disorders
N05z100	Osteoarthritis NOS, of shoulder region
N05zA00	Osteoarthritis NOS, of sternoclavicular joint
N050111	Heberdens' nodes
N050.00	Generalised osteoarthritis - OA
N053700	Localised osteoarthritis, unspecified, of the ankle and foot
N05z411	Finger osteoarthritis NOS
N05z713	Toe osteoarthritis NOS
N05z500	Osteoarthritis NOS, pelvic region/thigh
N05z.00	Osteoarthritis NOS
N05z900	Osteoarthritis NOS, of shoulder
N05zJ00	Osteoarthritis NOS, of hip
N05zS00	Osteoarthritis NOS, of 1st MTP joint
N05zF00	Osteoarthritis NOS, of MCP joint
N05zN00	Osteoarthritis NOS, of ankle
N05zT00	Osteoarthritis NOS, of lesser MTP joint
N05zE00	Osteoarthritis NOS, of wrist
N05zH00	Osteoarthritis NOS, of DIP joint of finger
N05zG00	Osteoarthritis NOS, of PIP joint of finger
N050500	Secondary multiple arthrosis
N05z800	Osteoarthritis NOS, other specified site
N05z600	Osteoarthritis NOS, of the lower leg
N05z311	Wrist osteoarthritis NOS
N053100	Localised osteoarthritis, unspecified, of shoulder region
N05z700	Osteoarthritis NOS, of ankle and foot
N051500	Localised, primary osteoarthritis of the pelvic region/thigh
N053400	Localised osteoarthritis, unspecified, of the hand
N053800	Localised osteoarthritis, unspecified, of other spec site
N051F00	Localised, primary osteoarthritis of elbow
N05zC00	Osteoarthritis NOS, of elbow
N051800	Localised, primary osteoarthritis of other specified site
N053500	Localised osteoarthritis, unspecified, pelvic region/thigh
N051z00	Localised, primary osteoarthritis NOS
N051600	Localised, primary osteoarthritis of the lower leg
N053900	Arthrosis of first carpometacarpal joint, unspecified
N051400	Localised, primary osteoarthritis of the hand
N054.00	Oligoarticular osteoarthritis, unspecified
N052400	Localised, secondary osteoarthritis of the hand
N050400	Primary generalized osteoarthrosis
N050200	Generalised osteoarthritis of multiple sites
N051100	Localised, primary osteoarthritis of the shoulder region

N051B00	Primary gonarthrosis, bilateral
N05z300	Osteoarthritis NOS, of the forearm
N051200	Localised, primary osteoarthritis of the upper arm
N051900	Primary coxarthrosis, bilateral
N052A00	Post-traumatic gonarthrosis, bilateral
N050700	Heberden's nodes with arthropathy
N051D00	Localised, primary osteoarthritis of the wrist
N051700	Localised, primary osteoarthritis of the ankle and foot
N051A00	Coxarthrosis resulting from dysplasia, bilateral
N05zU00	Osteoarthritis NOS, of IP joint of toe
N05zz00	Osteoarthritis NOS
N051E00	Localised, primary osteoarthritis of toe
N053z00	Localised osteoarthritis, unspecified, NOS
N051.00	Localised, primary osteoarthritis
N052800	Localised, secondary osteoarthritis of other specified site
N052600	Localised, secondary osteoarthritis of the lower leg
N052100	Localised, secondary osteoarthritis of the shoulder region
N05zK00	Osteoarthritis NOS, of sacro-iliac joint
N052700	Localised, secondary osteoarthritis of the ankle and foot
N053.00	Localised osteoarthritis, unspecified
N053600	Localised osteoarthritis, unspecified, of the lower leg
N051300	Localised, primary osteoarthritis of the forearm
N050z00	Generalised osteoarthritis NOS
N05z000	Osteoarthritis NOS, of unspecified site
N050112	Bouchards' nodes
N051C00	Primary arthrosis of first carpometacarpal joints, bilateral
N050100	Generalised osteoarthritis of the hand
N050300	Bouchard's nodes with arthropathy
N050600	Erosive osteoarthrosis
N050000	Generalised osteoarthritis of unspecified site
N05zP00	Osteoarthritis NOS, of subtalar joint
N052200	Localised, secondary osteoarthritis of the upper arm
N054600	Oligoarticular osteoarthritis, unspecified, of lower leg
N054800	Oligoarticular osteoarthritis, unspecified, other spec sites
N052.00	Localised, secondary osteoarthritis
N052500	Localised, secondary osteoarthritis of pelvic region/thigh
N052300	Localised, secondary osteoarthritis of the forearm
N054000	Oligoarticular osteoarthritis, unspec, of unspecified sites
N053000	Localised osteoarthritis, unspecified, of unspecified site
N052C00	Post-traumatic gonarthrosis, unilateral
N05z200	Osteoarthritis NOS, of the upper arm
N054100	Oligoarticular osteoarthritis, unspecified, of shoulder
N05z711	Ankle osteoarthritis NOS
N053511	Otto's pelvis
N054z00	Osteoarthritis of more than one site, unspecified, NOS
N051000	Localised, primary osteoarthritis of unspecified site
N05zR00	Osteoarthritis NOS, of other tarsal joint
N05zQ00	Osteoarthritis NOS, of talonavicular joint
N054900	Oligoarticular osteoarthritis, unspecified, multiple sites
N052z00	Localised, secondary osteoarthritis NOS
N054400	Oligoarticular osteoarthritis, unspecified, of hand
N053200	Localised osteoarthritis, unspecified, of the upper arm
N052B00	Post-traumatic arthrosis of first carpometacarpal jt bilat
N053300	Localised osteoarthritis, unspecified, of the forearm
N052900	Post-traumatic coxarthrosis, bilateral
N05zD00	Osteoarthritis NOS, of distal radio-ulnar joint

N054500	Oligoarticular osteoarthritis, unspecified, of pelvis/thigh
N052000	Localised, secondary osteoarthritis of unspecified site
N05zM00	Osteoarthritis NOS, of tibio-fibular joint
N054700	Oligoarticular osteoarthritis, unspecified, of ankle/foot
N054200	Oligoarticular osteoarthritis, unspecified, of upper arm
N052511	Coxae malum senilis
N051G00	Osteoarthritis of spinal facet joint

Appendix 2.2 Product Codes of the Gabapentinoids

BNF Code	Drug Name	Product Name
04030000/04070300/04080100	Pregabalin	Pregabalin 100mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 150mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 150mg/5ml oral solution
04030000/04070300/04080100	Pregabalin	Pregabalin 150mg/5ml oral suspension
04030000/04070300/04080100	Pregabalin	Pregabalin 200mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 225mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 25mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 300mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 50mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 50mg capsules (Accord Healthcare)
04030000/04070300/04080100	Pregabalin	Pregabalin 50mg capsules (Sandoz)
04030000/04070300/04080100	Pregabalin	Pregabalin 75mg capsules
04030000/04070300/04080100	Pregabalin	Pregabalin 75mg/5ml oral solution
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 100mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 150mg capsules (Lexon (UK))
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 150mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 150mg capsules (Sigma Pharmaceuticals Plc)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 200mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 20mg/ml oral solution (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 225mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 25mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 300mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 50mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 50mg capsules (Waymade Healthcare Plc)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 75mg capsules (Pfizer)
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 75mg capsules (Stephar (U.K.))
04030000/04070300/04080100/06010500	Pregabalin	Lyrica 75mg capsules (Waymade Healthcare Plc)
04030000/04070300/04080100/06010500	Pregabalin	Pregabalin 20mg/ml oral solution sugar free
04030000/04080100	Pregabalin	Alzain 100mg capsules (Dr Reddy's Laboratories (UK))

04030000/04080100	Pregabalin	Alzain 150mg capsules (Dr Reddy's Laboratories (UK))
04030000/04080100	Pregabalin	Alzain 200mg capsules (Dr Reddy's Laboratories (UK))
04030000/04080100	Pregabalin	Alzain 225mg capsules (Dr Reddy's Laboratories (UK))
04030000/04080100	Pregabalin	Alzain 25mg capsules (Dr Reddy's Laboratories (UK))
04030000/04080100	Pregabalin	Alzain 300mg capsules (Dr Reddy's Laboratories (UK))
04030000/04080100	Pregabalin	Alzain 50mg capsules (Dr Reddy's Laboratories (UK))
04030000/04080100	Pregabalin	Alzain 75mg capsules (Dr Reddy's Laboratories (UK))
04030000/04080100	Pregabalin	Lecaent 50mg capsules (Actavis UK)
04030000/04080100	Pregabalin	Pregabalin 100mg capsules (A A H Pharmaceuticals)
04030000/04080100	Pregabalin	Pregabalin 25mg capsules (Teva UK)
04030000/04080100	Pregabalin	Pregabalin 50mg capsules (A A H Pharmaceuticals)
04030000/04080100	Pregabalin	Pregabalin 75mg capsules (Teva UK)
04030000/04080100	Pregabalin	Rewisca 100mg capsules (Consilient Health)
04030000/04080100	Pregabalin	Rewisca 150mg capsules (Consilient Health)
04030000/04080100	Pregabalin	Rewisca 200mg capsules (Consilient Health)
04030000/04080100	Pregabalin	Rewisca 225mg capsules (Consilient Health)
04030000/04080100	Pregabalin	Rewisca 25mg capsules (Consilient Health)
04030000/04080100	Pregabalin	Rewisca 300mg capsules (Consilient Health)
04030000/04080100	Pregabalin	Rewisca 50mg capsules (Consilient Health)
04030000/04080100	Pregabalin	Rewisca 75mg capsules (Consilient Health)
04070300/04080100	Gabapentin	Gabapentin 100mg capsules
04070300/04080100	Gabapentin	Gabapentin 100mg capsules (A A H Pharmaceuticals)
04070300/04080100	Gabapentin	Gabapentin 100mg capsules (Actavis UK)
04070300/04080100	Gabapentin	Gabapentin 100mg capsules (Mylan)
04070300/04080100	Gabapentin	Gabapentin 100mg capsules (Sandoz)
04070300/04080100	Gabapentin	Gabapentin 100mg capsules (Teva UK)
04070300/04080100	Gabapentin	Gabapentin 100mg capsules (Zentiva)
04070300/04080100	Gabapentin	Gabapentin 100mg/5ml oral solution
04070300/04080100	Gabapentin	Gabapentin 250mg/5ml oral solution
04070300/04080100	Gabapentin	Gabapentin 250mg/5ml Oral solution (Boots Pharmaceuticals)
04070300/04080100	Gabapentin	Gabapentin 250mg/5ml oral suspension
04070300/04080100	Gabapentin	Gabapentin 300mg capsules

04070300/04080100	Gabapentin	Gabapentin 300mg capsules (A A H Pharmaceuticals)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Actavis UK)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Alliance Healthcare (Distribution))
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Arrow Generics)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Bristol Laboratories)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Creo Pharma)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Mylan)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Ranbaxy (UK))
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Sandoz)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Teva UK)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Waymade Healthcare Plc)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Zentiva)
04070300/04080100	Gabapentin	Gabapentin 300mg/5ml oral solution
04070300/04080100	Gabapentin	Gabapentin 300mg/5ml oral suspension
04070300/04080100	Gabapentin	Gabapentin 400mg capsules
04070300/04080100	Gabapentin	Gabapentin 400mg capsules (Almus Pharmaceuticals)
04070300/04080100	Gabapentin	Gabapentin 400mg/5ml oral solution
04070300/04080100	Gabapentin	Gabapentin 400mg/5ml oral suspension
04070300/04080100	Gabapentin	Gabapentin 50mg/ml oral solution sugar free
04070300/04080100	Gabapentin	Gabapentin 50mg/ml oral solution sugar free (Alliance Healthcare (Distribution))
04070300/04080100	Gabapentin	Gabapentin 600mg tablets
04070300/04080100	Gabapentin	Gabapentin 600mg tablets (A A H Pharmaceuticals)
04070300/04080100	Gabapentin	Gabapentin 600mg tablets (DE Pharmaceuticals)
04070300/04080100	Gabapentin	Gabapentin 600mg tablets (Teva UK)
04070300/04080100	Gabapentin	Gabapentin 600mg tablets (Zentiva)
04070300/04080100	Gabapentin	Gabapentin 600mg/5ml oral solution
04070300/04080100	Gabapentin	Gabapentin 800mg tablets
04070300/04080100	Gabapentin	Neurontin 100mg capsules (Pfizer)
04070300/04080100	Gabapentin	Neurontin 300mg capsules (Dowelhurst)
04070300/04080100	Gabapentin	Neurontin 300mg capsules (Pfizer)
04070300/04080100	Gabapentin	Neurontin 400mg capsules (Pfizer)
04070300/04080100	Gabapentin	Neurontin 600mg tablets (Pfizer)

04070300/04080100	Gabapentin	Neurontin 800mg tablets (Pfizer)
4070300	Gabapentin	Gabapentin 6% gel
4080100	Gabapentin	Gabapentin 600mg tablets and Gabapentin 300mg capsules
04070300/04080100	Gabapentin	Gabapentin 100mg capsules (Generics (UK) Ltd)
04070300/04080100	Gabapentin	Gabapentin 300mg capsules (Generics (UK) Ltd)

Appendix 2.3 Read Codes of Hip and Knee Arthroplasty

Read Code	Read Term
7K20.16	Freeman total replacement of hip joint using cement
7K20000	Primary cemented total hip replacement
7K20.1G	THR - Total prosthetic replacement of hip joint using cement
7K21.13	Lord total replacement of hip joint not using cement
7K21.15	Monk total replacement of hip joint not using cement
7K20.1C	Muller total replacement of hip joint using cement
7K22.12	THR - Other total prosthetic replacement of hip joint
7K22000	Primary total prosthetic replacement of hip joint NEC
7K20.17	Furlong total replacement of hip joint using cement
7K21.16	Ring total replacement of hip joint not using cement
7K20.11	Arthroplasty of hip joint using cement
7K21.12	Furlong total replacement of hip joint not using cement
7K21.11	Freeman total replacement of hip joint not using cement
7K20.1F	Turner total replacement of hip joint using cement
7K20.1A	McKee total replacement of hip joint using cement
7K20.12	Aufranc total replacement of hip joint using cement
7K21.17	THR - Total prosthetic replacement hip joint without cement
7K21.00	Total prosthetic replacement of hip joint not using cement
7K20.14	Exeter total replacement of hip joint using cement
7K20.1D	Pretoria total replacement of hip joint using cement
7K20.19	Ilch total replacement of hip joint using cement
7K21.14	Madreporique total replacement of hip joint not using cement
7K20.18	Howse total replacement of hip joint using cement
7K20.1E	Stanmore total replacement of hip joint using cement
7K22.00	Other total prosthetic replacement of hip joint
7K20300	Primary hybrid total replacement of hip joint NEC
7K20.1B	Monk total replacement of hip joint using cement
7K20.13	Charnley total replacement of hip joint using cement
7K20.00	Total prosthetic replacement of hip joint using cement
7K20.15	Farrer total replacement of hip joint using cement
7K20011	Charnley cemented total hip replacement
7K21y00	Other specified total prosthetic replacement of hip joint not using cement
7K20y00	Other specified total prosthetic replacement of hip joint using cement
7K21000	Primary uncemented total hip replacement
7K21z00	Total prosthetic replacement of hip joint not using cement NOS
7K20z00	Total prosthetic replacement of hip joint using cement NOS
7K22z00	Total prosthetic replacement of hip joint NOS
7K30.00	Total prosthetic replacement of knee joint using cement
7K30.11	Anametric total replacement of knee joint using cement
7K30.13	Attenborough total replacement of knee joint using cement
7K30.15	Cavendish total replacement of knee joint using cement
7K30.16	Charnley total replacement of knee joint using cement
7K30.17	Deane total replacement of knee joint using cement
7K30.18	Denham total replacement of knee joint using cement
7K30.19	Freeman total replacement of knee joint using cement
7K30.1A	Geomedic total replacement of knee joint using cement
7K30.1B	Geometric total replacement of knee joint using cement
7K30.1C	Guepar hinge replacement of knee joint using cement
7K30.1D	Gunston total replacement of knee joint using cement
7K30.1E	Herbert total replacement of knee joint using cement
7K30.1F	Ilch total replacement of knee joint using cement
7K30.1G	Irving total replacement of knee joint using cement
7K30.1H	Liverpool total replacement of knee joint using cement

7K30.1I	Manchester total replacement of knee joint using cement
7K30.1J	Marmor total replacement of knee joint using cement
7K30.1L	Melbourne total replacement of knee joint using cement
7K30.1N	Polycentric total replacement of knee joint using cement
7K30.1P	Sheehan total replacement of knee joint using cement
7K30.1Q	Shiers total replacement of knee joint using cement
7K30.1R	Stanmore total replacement of knee joint using cement
7K30.1S	Swanson total replacement of knee joint using cement
7K30.1T	Uci total replacement of knee joint using cement
7K30.1V	TKR -Total prosthetic replacement of knee joint using cement
7K31.00	Total prosthetic replacement of knee joint not using cement
7K31.12	TKR - Total prosthetic replacement knee joint without cement
7K32.00	Other total prosthetic replacement of knee joint
7K32.12	TKR - Other total prosthetic replacement of knee joint
7K32000	Primary total knee replacement NEC
7K32011	Primary hybrid total knee replacement NEC
K812	TOTAL KNEE REPLACEMENT
7K30000	Primary cemented total knee replacement
7K30y00	Total prosthetic replacement of knee joint using cement OS
7K30z00	Total prosthetic replacement of knee joint using cement NOS
7K31000	Primary uncemented total knee replacement
7K31y00	Total prosthetic replacement knee joint not using cement OS
7K31z00	Total prosthetic replacement knee joint not using cement NOS
7K32y00	Other total prosthetic replacement of knee joint OS
7K32z00	Other total prosthetic replacement of knee joint NOS

Appendix 2.4 Read Codes of Identified Licensed and Unlicensed Gabapentinoid Indications

Epilepsy

Read Code	Read Term
2126000	Epilepsy resolved
F132100	Progressive myoclonic epilepsy
F25..00	Epilepsy
F250.00	Generalised nonconvulsive epilepsy
F250000	Petit mal (minor) epilepsy
F250011	Epileptic absences
F250100	Pykno-epilepsy
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F250400	Juvenile absence epilepsy
F250500	Lennox-Gastaut syndrome
F250y00	Other specified generalised nonconvulsive epilepsy
F250z00	Generalised nonconvulsive epilepsy NOS
F251.00	Generalised convulsive epilepsy
F251000	Grand mal (major) epilepsy
F251011	Tonic-clonic epilepsy
F251100	Neonatal myoclonic epilepsy
F251111	Otohara syndrome
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251500	Tonic-clonic epilepsy
F251y00	Other specified generalised convulsive epilepsy
F251z00	Generalised convulsive epilepsy NOS
F252.00	Petit mal status
F253.00	Grand mal status
F253.11	Status epilepticus
F254.00	Partial epilepsy with impairment of consciousness
F254000	Temporal lobe epilepsy
F254100	Psychomotor epilepsy
F254200	Psychosensory epilepsy
F254300	Limbic system epilepsy
F254400	Epileptic automatism
F254500	Complex partial epileptic seizure
F254z00	Partial epilepsy with impairment of consciousness NOS
F255.00	Partial epilepsy without impairment of consciousness
F255000	Jacksonian; focal or motor epilepsy
F255011	Focal epilepsy
F255012	Motor epilepsy
F255100	Sensory induced epilepsy
F255200	Somatosensory epilepsy
F255300	Visceral reflex epilepsy
F255311	Partial epilepsy with autonomic symptoms
F255400	Visual reflex epilepsy
F255500	Unilateral epilepsy
F255600	Simple partial epileptic seizure
F255y00	Partial epilepsy without impairment of consciousness OS
F255z00	Partial epilepsy without impairment of consciousness NOS
F256.00	Infantile spasms
F256000	Hypsarrhythmia

F256100	Salaam attacks
F256.11	Lightning spasms
F256.12	West syndrome
F256z00	Infantile spasms NOS
F257.00	Kojevnikov's epilepsy
F258.00	Post-ictal state
F259.00	Early infant epileptic encephalopathy wth suppression bursts
F259.11	Ohtahara syndrome
F25A.00	Juvenile myoclonic epilepsy
F25B.00	Alcohol-induced epilepsy
F25C.00	Drug-induced epilepsy
F25D.00	Menstrual epilepsy
F25E.00	Stress-induced epilepsy
F25F.00	Photosensitive epilepsy
F25X.00	Status epilepticus; unspecified
F25y.00	Other forms of epilepsy
F25y000	Cursive (running) epilepsy
F25y100	Gelastic epilepsy
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
F25y300	Complex partial status epilepticus
F25y400	Benign Rolandic epilepsy
F25y500	Panayiotopoulos syndrome
F25yz00	Other forms of epilepsy NOS
F25z.00	Epilepsy NOS
SC20000	Traumatic epilepsy
1B1W.00	Transient epileptic amnesia
1O30.00	Epilepsy confirmed
2824.11	O/E - Jacksonian fit
667B.00	Nocturnal epilepsy
667N.00	Epilepsy severity
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]
F132200	Myoclonic encephalopathy
F251600	Grand mal seizure
F25G.00	Severe myoclonic epilepsy in infancy
Fyu5000	[X]Other generalized epilepsy and epileptic syndromes
Fyu5100	[X]Other epilepsy
Fyu5200	[X]Other status epilepticus
Fyu5900	[X]Status epilepticus; unspecified
ZS82.00	Acquired epileptic aphasia
ZS82.11	Landau-Kleffner syndrome
212J.00	Epilepsy resolved
667..00	Epilepsy monitoring
667A.00	Epilepsy treatment stopped
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

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
F25z.11	Fit (in known epileptic) NOS
F25G.11	Dravet syndrome
F25H.00	Generalised seizure

Generalised Anxiety Disorder

Read Code	Read Term
E200200	Generalised anxiety disorder
Eu41100	[X]Generalized anxiety disorder

Neuropathic Pain

Read Code	Read Term
C106.00	Diabetes mellitus with neurological manifestation
C106100	Diabetes mellitus; adult onset; + neurological manifestation
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C106y00	Other specified diabetes mellitus with neurological comps
C106z00	Diabetes mellitus NOS with neurological manifestation
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
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
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
C10E200	Type 1 diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
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

C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
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
F345000	Diabetic mononeuritis multiplex
F35z000	Diabetic mononeuritis NOS
F372000	Acute painful diabetic neuropathy
F372100	Chronic painful diabetic neuropathy
F372.11	Diabetic polyneuropathy
F372.12	Diabetic neuropathy
F372200	Asymptomatic diabetic neuropathy
F3y0.00	Diabetic mononeuropathy
C106.11	Diabetic amyotrophy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
F374z00	Polyneuropathy in disease NOS
F381300	Myasthenic syndrome due to diabetic amyotrophy
F381311	Diabetic amyotrophy
F171100	Autonomic neuropathy due to diabetes
F372.00	Polyneuropathy in diabetes
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
F171z00	Peripheral autonomic neuropathy due to disease NOS
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C108211	Type I diabetes mellitus with neurological complications
M271100	Neuropathic diabetic ulcer - foot
A531.11	Post-herpetic neuralgia
A531100	Geniculate herpes zoster
A531111	Ramsey - Hunt syndrome
A531300	Postherpetic polyneuropathy
A531500	Postzoster neuralgia
A531511	Postherpetic neuralgia
F311.00	Geniculate ganglionitis
F374400	Polyneuropathy in herpes zoster
A531.11	Post-herpetic neuralgia
A531200	Postherpetic trigeminal neuralgia
A531300	Postherpetic polyneuropathy
A531500	Postzoster neuralgia
A531511	Postherpetic neuralgia
F300.00	Post-herpetic trigeminal neuralgia
F374400	Polyneuropathy in herpes zoster
A53..00	Herpes zoster
A53..11	Shingles
A530.00	Herpes zoster with meningitis
A531z00	Herpes zoster with other CNS complication NOS
A532.00	Herpes zoster with ophthalmic complication

A532000	Herpes zoster with dermatitis of eyelid
A532100	Herpes zoster with keratoconjunctivitis
A532200	Herpes zoster iridocyclitis
A532300	Ophthalmic herpes zoster infection
A532400	Herpes zoster ophthalmicus
A532z00	Herpes zoster with other ophthalmic complication
A53x.00	Herpes zoster with other specified complication
A53x000	Herpes zoster otitis externa
A53x100	Disseminated zoster
A53xz00	Herpes zoster with other specified complication NOS
A53y.00	Herpes zoster with unspecified complication
A53z.00	Herpes zoster NOS
AyuA500	[X]Zoster without complications
F501600	Infective otitis externa due to herpes zoster
F501611	Herpes zoster - otitis externa
F366.00	Polyneuropathy
F367.00	Peripheral neuropathy
F370100	Postinfectious polyneuritis
F374.00	Polyneuropathy in disease EC
F374z00	Polyneuropathy in disease NOS
F37z.11	Polyneuropathy unspecified
Fyu6A00	[X]Other mononeuropathies of upper limb
Fyu6B00	[X]Other mononeuropathies of lower limb
Fyu6C00	[X]Other specified mononeuropathies
Fyu6D00	[X]Other mononeuropathies in diseases classified elsewhere
Fyu7.00	[X]Polyneuropathies & other disord of peripheral nerv syst
Fyu7200	[X]Other specified polyneuropathies
Fyu7500	[X]Polyneuropathy/other endocrine+metabolic diseases CE
Fyu7C00	[X] Polyneuropathy, unspecified
N035.00	Neuropathic arthropathy
N035.11	Charcot's arthropathy
N035.12	Neuropathic arthritis
N242.00	Neuralgia, neuritis and radiculitis unspecified
N242000	Neuralgia unspecified
N242z00	Neuralgia, neuritis or radiculitis NOS
N242z11	Policeman's disease
N242300	Neuropathic pain
A531200	Postherpetic trigeminal neuralgia
F300.00	Post-herpetic trigeminal neuralgia
F301.00	Other specified trigeminal neuralgia
F301000	Tic douloureux
F301z00	Trigeminal neuralgia NOS
F30y.00	Other trigeminal nerve disorder
1475	H/O: trigeminal neuralgia
F30..00	Trigeminal nerve disorders
F336000	Phantom limb syndrome with pain
F336100	Phantom limb syndrome without pain
F336.00	Phantom limb syndrome
F262100	Horton's (histamine) neuralgia
F262500	Periodic migrainous neuralgia
F321.00	Glossopharyngeal neuralgia
F356100	Morton's neuralgia
FyuJ100	[X]Retrobulbar neuritis in diseases classified elsewhere
N142000	Lumbago with sciatica
N143.00	Sciatica
N143.11	Acute back pain with sciatica

F256000	Hypsarrhythmia
F371200	Polyneuropathy in rheumatoid arthritis
F375.00	Alcoholic polyneuropathy
29B2.00	O/E - anaesthesia present
29B2000	O/E - anaesthesia in legs
29B2100	O/E - anaesthesia of extremities
29B2.11	O/E - loss of touch sensation
29B3.00	O/E - hypoaesthesia present
29B4.00	O/E - hyperaesthesia present
29B8.00	10g monofilament sensation absent
29B9.00	10g monofilament sensation R foot abnormal
29BA.00	10g monofilament sensation L foot abnormal
29H2.00	O/E - vibration sense reduced
29H3.00	O/E - vibration sense absent
29H4.00	O/E - Vibration sense of right foot abnormal
29H6.00	O/E - Vibration sense of left foot abnormal
29H8.00	O/E - vibration sense left foot reduced
29H9.00	O/E - vibration sense right foot reduced
29HA.00	O/E - Vibration sense of right foot absent
29HB.00	O/E - Vibration sense of left foot absent
F161400	Subacute necrotic myelopathy
F163.00	Myelopathy due to disease EC
F163000	Myelopathy due to intervertebral disc disease
F163200	Myelopathy due to spondylosis
F163z00	Myelopathy due to disease NOS
F16y.00	Other myelopathy
F16y000	Drug induced myelopathy
F16y100	Radiation induced myelopathy
F16yz00	Other myelopathy NOS
F16z.00	Myelopathy NOS
F16z.11	Cord compression NOS
F16z.12	Spinal cord compression NOS
F246.00	Cauda equina syndrome
F246000	Cauda equina syndrome not affecting bladder
F246100	Cauda equina syndrome with cord bladder
F246z00	Cauda equina syndrome NOS
F29y400	Cord compression
F29y411	Spinal cord compression
F337100	Nerve root and plexus compressions in intervert disc disord
F337200	Nerve root and plexus compressions in spondylosis
F337300	Nerve root and plexus compressions in other dorsopathies
F350.00	Sciatic nerve lesion
F378.00	Intercostal neuropathy
N113.00	Thoracic spondylosis with myelopathy
N113000	Single-level thoracic spondylosis with myelopathy
N113200	Multiple-level thoracic spondylosis with myelopathy
N115.00	Lumbosacral spondylosis with myelopathy
N115000	Single-level lumbosacral spondylosis with myelopathy
N115100	Two-level lumbosacral spondylosis with myelopathy
N115200	Multiple-level lumbosacral spondylosis with myelopathy
N11B.00	Thoracic spondylosis with radiculopathy
N11B000	Single-level thoracic spondylosis with radiculopathy
N11B100	Two-level thoracic spondylosis with radiculopathy
N11B200	Multiple-level thoracic spondylosis with radiculopathy
N11C.00	Lumbosacral spondylosis with radiculopathy
N11C000	Single-level lumbosacral spondylosis with radiculopathy

N11C100	Two-level lumbosacral spondylosis with radiculopathy
N11C200	Multiple-level lumbosacral spondylosis with radiculopathy
N11y200	Neuropathic spondylopathy
N11z100	Spondylosis with myelopathy, NOS
N129.00	Disc disorder with myelopathy
N129.11	Prolapsed intervertebral disc with associated myelopathy
N129000	Unspecified disc disorder with myelopathy
N129200	Thoracic disc disorder with myelopathy
N129300	Lumbar disc disorder with myelopathy
N129z00	Disc disorder with myelopathy NOS
N12B.00	Disc prolapse with myelopathy
N12B100	Thoracic disc prolapse with myelopathy
N12B200	Lumbar disc prolapse with myelopathy
N12C400	Prolapsed lumbar intervertebral disc with sciatica
N134.11	Brachial radiculitis
N144.00	Thoracic and lumbosacral neuritis
N144000	Thoracic neuritis, unspecified
N144100	Lumbosacral neuritis, unspecified
N144z00	Thoracic and lumbosacral neuritis NOS
Nyu6200	[X]Other spondylosis with myelopathy
Nyu6300	[X]Other spondylosis with radiculopathy
Nyu7300	[X]Lumbar + other intervertebral disc disorders with myelopathy
Nyu7400	[X]Lumbar + other intervertebral disc disorders with radiculopathy
F330300	Thoracic Outlet Syndrome
N111.00	Cervical spondylosis with myelopathy
N111000	Single-level cervical spondylosis with myelopathy
N111100	Two-level cervical spondylosis with myelopathy
N111200	Multiple-level cervical spondylosis with myelopathy
N111300	Cervical myelopathy
N119.00	Cervical spondylosis with radiculopathy
N119000	Single-level cervical spondylosis with radiculopathy
N119100	Two-level cervical spondylosis with radiculopathy
N119200	Multiple-level cervical spondylosis with radiculopathy
N129100	Cervical disc disorder with myelopathy
N12B000	Cervical disc prolapse with myelopathy
N12zH00	Cervical disc disorder with radiculopathy
N134.00	Brachial (cervical) neuritis
N134.12	Cervical radiculitis
F337000	Nerve root and plexus compressions in neoplastic disease
F373.00	Polyneuropathy in malignant disease
F344.00	Causalgia
N337.12	Reflex sympathetic dystrophy
N337111	Reflex sympathetic dystrophy
F302.00	Atypical face pain
1B46.00	C/O paraesthesia
29B5.00	O/E - paraesthesia present
29B5000	O/E - paraesthesia in hands
A72x100	Mumps polyneuropathy
C262300	Burning feet syndrome
C34y400	Gouty neuritis
F335.00	Neuralgia amyotrophy
F335.11	Parsonage - Aldren - Turner syndrome
F342.11	Neuritis ulnar nerve
F342000	Cubital tunnel syndrome
F370z00	Acute infective polyneuritis NOS
FyuAE00	[X]Myelopathy in diseases classified elsewhere

G73y400	Acroparaesthesia - Schultze's type
G73y500	Acroparaesthesia - Nothnagel's type
G73y511	Nothnagel's vasomotor acroparaesthesia
G73y600	Acroparaesthesia - unspecified
R020700	[D]Paraesthesia
E011100	Korsakov's alcoholic psychosis with peripheral neuritis
F33..00	Nerve root and plexus disorders
F337.00	Nerve root and plexus compressions in diseases EC
F33y.00	Other nerve root or plexus disorder
F33z.00	Nerve root or plexus disorder NOS
F34..00	Mononeuritis of upper limb and mononeuritis multiplex
F340.00	Carpal tunnel syndrome
F340.12	CTS- Carpal tunnel syndrome
F341000	Median nerve neuritis
F341100	Median nerve compression in forearm
F345.00	Mononeuritis multiplex
F34y.00	Other upper limb mononeuritis
F34z.00	Mononeuritis upper limb NOS
F35..00	Mononeuritis lower limb
F351.00	Meralgia paraesthetica
F355.00	Tarsal tunnel syndrome
F356000	Morton's metatarsalgia
F35x.00	Other mononeuritis lower limb
F35y.00	Unspecified mononeuritis lower limb
F35z.00	Mononeuritis of unspecified site NOS
F35z.11	Peripheral neuropathy - hereditary or idiopathic
F36..00	Hereditary and idiopathic peripheral neuropathy
F360.00	Hereditary peripheral neuropathy
F360z00	Hereditary peripheral neuropathy NOS
F362.00	Hereditary sensory neuropathy
F364.00	Idiopathic progressive polyneuropathy
F365.00	Neuropathy in association with hereditary ataxia
F36y.00	Other idiopathic peripheral neuropathy
F36yz00	Other idiopathic peripheral neuropathy NOS
F36z.00	Hereditary or idiopathic peripheral neuropathy NOS
F37..00	Inflammatory and toxic neuropathy
F37..11	Toxic neuropathy
F370.00	Acute infective polyneuritis
F371.00	Polyneuropathy in collagen vascular disease
F371000	Polyneuropathy in disseminated lupus erythematosus
F371100	Polyneuropathy in polyarteritis nodosa
F371z00	Polyneuropathy in collagen vascular disease NOS
F374000	Polyneuropathy in amyloidosis
F374100	Polyneuropathy in beriberi
F374200	Polyneuropathy in vitamin B deficiency
F374300	Polyneuropathy in diphtheria
F374500	Polyneuropathy in hypoglycaemia
F374600	Polyneuropathy in mumps
F374800	Polyneuropathy in porphyria
F374900	Polyneuropathy in sarcoidosis
F374A00	Polyneuropathy in uraemia
F376.00	Polyneuropathy due to drugs
F377.00	Other toxic agent polyneuropathy
F37y.00	Other toxic or inflammatory neuropathy
F37y000	Serum neuropathy
F37z.00	Toxic or inflammatory neuropathy NOS

Fyu1300	[X]Paraneoplastic neuromyopathy and neuropathy
Fyu6.00	[X]Nerve, nerve root and plexus disorders
Fyu6500	[X]Other nerve root and plexus disorders
Fyu7100	[X}Other inflammatory polyneuropathies
Fyu7800	[X]Polyneuropathy/other musculoskeletal disorders CE
Fyu7B00	[X]Inflammatory polyneuropathy, unspecified
FyuAC00	[X]Autonomic neuropathy/endocrine+metabolic disease
L164.00	Peripheral neuritis in pregnancy
N134.14	Ulnar neuritis
N1y0.00	Recurrent atlantoaxial subluxation with myelopathy
N242100	Neuritis unspecified
N242200	Radiculitis unspecified
F37y100	Axonal sensorimotor neuropathy
F330.00	Brachial plexus lesions
F330000	Cervical rib syndrome

Alcohol Withdrawal

Read Code	Read Term
Eu10800	[X]Alcohol withdrawal-induced seizure
E01y000	Alcohol withdrawal syndrome

Attention Deficit Disorder

Read Code	Read Term
Eu90000	[X]Disturbance of activity and attention
Eu90011	[X]Attention deficit hyperactivity disorder
E2E0.00	Child attention deficit disorder
Eu9y700	[X]Attention deficit disorder
E2E0100	Attention deficit with hyperactivity
6A61.00	Attention deficit hyperactivity disorder annual review
ZS91.11	ADD - Attention deficit disorder
ZS91.00	Attention deficit disorder
Eu90.00	[X]Hyperkinetic disorders
Ry13.00	[D]Overactivity
E2E0z00	Child attention deficit disorder NOS
E2E2.00	Hyperkinetic conduct disorder
ZS91.12	[X]Attention deficit disorder
Eu90100	[X]Hyperkinetic conduct disorder
ZS9..00	Disorders of attention and motor control
E2E0000	Attention deficit without hyperactivity
Eu90z00	[X]Hyperkinetic disorder, unspecified
E2Ez.00	Hyperkinetic syndrome NOS
ZS94.00	Minimal brain dysfunction
E2E1.00	Hyperkinesis with developmental delay
Eu90111	[X]Hyperkinetic disorder associated with conduct disorder
Eu90y00	[X]Other hyperkinetic disorders
Eu90z12	[X]Hyperkinetic syndrome NOS

Bipolar Disorder

Read Code	Read Term
146D.00	H/O: manic depressive disorder
1S42.00	Manic mood
6657.11	Lithium monitoring
6657.12	Started lithium
E11..00	Affective psychoses
E110.00	Manic disorder; single episode
E110000	Single manic episode; unspecified
E110100	Single manic episode; mild
E110.11	Hypomanic psychoses
E110200	Single manic episode; moderate
E110300	Single manic episode; severe without mention of psychosis
E110400	Single manic episode; severe; with psychosis
E110600	Single manic episode in full remission
E110z00	Manic disorder; single episode NOS
E111.00	Recurrent manic episodes
E111000	Recurrent manic episodes; unspecified
E11..11	Bipolar psychoses
E111100	Recurrent manic episodes; mild
E111200	Recurrent manic episodes; moderate
E11..13	Manic psychoses
E111300	Recurrent manic episodes; severe without mention psychosis
E111400	Recurrent manic episodes; severe; with psychosis
E111500	Recurrent manic episodes; partial or unspecified remission
E111600	Recurrent manic episodes; in full remission
E111z00	Recurrent manic episode NOS
E114.00	Bipolar affective disorder; currently manic
E114000	Bipolar affective disorder; currently manic; unspecified
E114100	Bipolar affective disorder; currently manic; mild
E114.11	Manic-depressive - now manic
E114200	Bipolar affective disorder; currently manic; moderate
E114300	Bipolar affect disord; currently manic; severe; no psychosis
E114400	Bipolar affect disord; currently manic;severe with psychosis
E114500	Bipolar affect disord;currently manic; part/unspec remission
E114600	Bipolar affective disorder; currently manic; full remission
E114z00	Bipolar affective disorder; currently manic; NOS
E115.00	Bipolar affective disorder; currently depressed
E115000	Bipolar affective disorder; currently depressed; unspecified
E115100	Bipolar affective disorder; currently depressed; mild
E115.11	Manic-depressive - now depressed
E115200	Bipolar affective disorder; currently depressed; moderate
E115300	Bipolar affect disord; now depressed; severe; no psychosis
E115400	Bipolar affect disord; now depressed; severe with psychosis
E115500	Bipolar affect disord; now depressed; part/unspec remission
E115600	Bipolar affective disorder; now depressed; in full remission
E115z00	Bipolar affective disorder; currently depressed; NOS
E116.00	Mixed bipolar affective disorder
E116000	Mixed bipolar affective disorder; unspecified
E116100	Mixed bipolar affective disorder; mild
E116200	Mixed bipolar affective disorder; moderate
E116300	Mixed bipolar affective disorder; severe; without psychosis
E116400	Mixed bipolar affective disorder; severe; with psychosis
E116500	Mixed bipolar affective disorder; partial/unspec remission

E116600	Mixed bipolar affective disorder; in full remission
E116z00	Mixed bipolar affective disorder; NOS
E117.00	Unspecified bipolar affective disorder
E117000	Unspecified bipolar affective disorder; unspecified
E117100	Unspecified bipolar affective disorder; mild
E117200	Unspecified bipolar affective disorder; moderate
E117300	Unspecified bipolar affective disorder; severe; no psychosis
E117400	Unspecified bipolar affective disorder;severe with psychosis
E117500	Unspecified bipolar affect disord; partial/unspec remission
E117600	Unspecified bipolar affective disorder; in full remission
E117z00	Unspecified bipolar affective disorder; NOS
E11y.00	Other and unspecified manic-depressive psychoses
E11y000	Unspecified manic-depressive psychoses
E11y100	Atypical manic disorder
E11y300	Other mixed manic-depressive psychoses
E11yz00	Other and unspecified manic-depressive psychoses NOS
Eu3..00	[X]Mood - affective disorders
Eu30.00	[X]Manic episode
Eu30000	[X]Hypomania
Eu30100	[X]Mania without psychotic symptoms
Eu30.11	[X]Bipolar disorder; single manic episode
Eu30200	[X]Mania with psychotic symptoms
Eu30211	[X]Mania with mood-congruent psychotic symptoms
Eu30212	[X]Mania with mood-incongruent psychotic symptoms
Eu30y00	[X]Other manic episodes
Eu30z00	[X]Manic episode; unspecified
Eu30z11	[X]Mania NOS
Eu31.00	[X]Bipolar affective disorder
Eu31000	[X]Bipolar affective disorder; current episode hypomanic
Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu31.11	[X]Manic-depressive illness
Eu31.12	[X]Manic-depressive psychosis
Eu31.13	[X]Manic-depressive reaction
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu31400	[X]Bipol aff disord; curr epis sev depress; no psychot symp
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu31600	[X]Bipolar affective disorder; current episode mixed
Eu31700	[X]Bipolar affective disorder; currently in remission
Eu31y00	[X]Other bipolar affective disorders
Eu31y11	[X]Bipolar II disorder
Eu31y12	[X]Recurrent manic episodes
Eu31z00	[X]Bipolar affective disorder; unspecified
Eu33213	[X]Manic-depress psychosis;depressd;no psychotic symptoms
Eu33312	[X]Manic-depress psychosis;depressed type+psychotic symptoms
Eu34.00	[X]Persistent mood affective disorders
Eu34000	[X]Cyclothymia
Eu34y00	[X]Other persistent mood affective disorders
Eu34z00	[X]Persistent mood affective disorder; unspecified
Eu3y.00	[X]Other mood affective disorders
Eu3y000	[X]Other single mood affective disorders
Eu3y011	[X]Mixed affective episode
Eu3y100	[X]Other recurrent mood affective disorders
Eu3yy00	[X]Other specified mood affective disorders
Eu3z.00	[X]Unspecified mood affective disorder
Eu3z.11	[X]Affective psychosis NOS

ZV11111	[V]Personal history of manic-depressive psychosis
ZV11112	[V]Personal history of manic-depressive psychosis

Complex Regional Pain Syndrome

Read Code	Read Term
F369.00	Complex Regional Pain Syndrome
F369.11	Chronic Regional Pain Syndrome
N33C.00	Complex regional pain syndrome type I
F347.00	Complex regional pain syndrome type II
N337.00	Algoneurodystrophy
N337.11	Algodystrophy
N337.12	Reflex sympathetic dystrophy
N337111	Reflex Sympathetic dystrophy

Fibromyalgia

Read Code	Read Term
N239.00	Fibromyalgia
N248.00	Fibromyalgia

Menopausal Hot Flushes

Read Code	Read Term
K5A2000	Menopausal flushing
K5A2011	Hot flushes - menopausal

Migraine

Read Code	Read Term
1474000	H/O migraine with aura
8B6N.00	Migraine prophylaxis
F26..00	Migraine
F260.00	Classical migraine
F260.11	Migraine with aura
F261.00	Common migraine
F261000	Atypical migraine
F261.11	Migraine without aura
F261z00	Common migraine NOS
F262.00	Migraine variants
F262200	Abdominal migraine
F262300	Basilar migraine
F262400	Ophthalmic migraine
F262500	Periodic migrainous neuralgia

F262800	Migraine induced by oestrogen contraceptive
F262z00	Migraine variant NOS
F26y.00	Other forms of migraine
F26y000	Hemiplegic migraine
F26y100	Ophthalmoplegic migraine
F26y111	Moebius' ophthalmoplegic migraine
F26y200	Status migrainosus
F26y300	Complicated migraine
F26yz00	Other forms of migraine NOS
F26z.00	Migraine NOS
Fyu5300	[X]Other migraine
K584.11	Migraine - menstrual
R090D00	[D]Abdominal migraine

Panic Disorder

Read Code	Read Term
225J.00	O/E - panic attack
E200100	Panic disorder
E200111	Panic attack
E202.11	Social phobic disorders
E202300	Social phobia; fear of eating in public
E202400	Social phobia; fear of public speaking
E202500	Social phobia; fear of public washing
E280.00	Acute panic state due to acute stress reaction
Eu40100	[X]Social phobias
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]
Eu41011	[X]Panic attack
Eu41012	[X]Panic state

Restless Legs Syndrome

Read Code	Read Term
F13z200	Restless Legs Syndrome

Appendix 3 Surplus Results

Appendix 3.1 First Gabapentinoids Prescribed to Patients with OA, All Formulations

Gabapentin		Pregabalin	
Formulation	Frequency	Formulation	Frequency
Gabapentin 300mg capsules	12,932	Pregabalin 75mg capsules	2,871
Gabapentin 100mg capsules	11,433	Pregabalin 25mg capsules	2,733
Gabapentin 600mg capsules	413	Pregabalin 50mg capsules	2,273
Gabapentin 400mg capsules	238	Pregabalin 150mg capsules	517
Neurontin 300mg capsules	61	Pregabalin 100mg capsules	378
Gabapentin 800mg capsules	51	Pregabalin 300mg capsules	267
Neurontin 100mg capsules	33	Lyrica 25mg capsules	222
Gabapentin 50mg/ml solution	14	Lyrica 75mg capsules	191
Gabapentin 250mg/5ml solution	10	Lyrica 50mg capsules	158
Neurontin 600mg capsules	9	Pregabalin 200mg capsules	98
Gabapentin 400mg/5ml solution	7	Lyrica 150mg capsules	44
Neurontin 400mg capsules	3	Pregabalin 225mg capsules	29
Gabapentin 300mg capsules (Teva UK Ltd)	2	Lyrica 300mg capsules	14
Neurontin 800mg capsules	1	Lyrica 100mg capsules	14
Gabapentin 100mg capsules (Teva UK Ltd)	1	Lyrica 200mg capsules	5
		Pregabalin 20mg/ml solution	4
		Rewisca 25mg capsules (Consilient Health Ltd)	2
		Lyrica 20mg/ml solution	1
		Alzain 25mg capsules (Dr Reddy's Laboratories (UK) Ltd)	1
		Alzain 150mg capsules (Dr Reddy's Laboratories (UK) Ltd)	1
Total	*25,208*	*Total*	*9,823*

Appendix 3.2 Number of Practices Contributing Patients Newly Diagnosed with OA to the CPRD, by Calendar Year

Region	Calendar Year																				
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
North East	4	4	4	5	7	7	9	8	9	9	10	10	10	10	10	10	10	9	8	6	4
North West	28	29	31	32	37	41	46	51	61	70	75	75	76	77	77	75	72	69	67	62	49
Yorkshire & The Humber	16	16	16	16	19	20	23	22	21	22	24	24	22	21	17	15	14	9	6	4	4
East Midlands	13	13	14	14	14	17	18	21	21	22	21	20	21	20	18	15	10	8	5	1	0
West Midlands	18	18	19	19	23	31	33	36	44	47	49	50	53	53	55	54	53	52	49	44	35
East of England	15	16	17	19	20	22	30	35	38	43	46	48	47	44	42	40	36	33	29	25	21
South West	19	19	20	22	26	28	31	39	41	44	49	51	52	52	54	54	51	49	46	37	27
South Central	11	11	12	12	13	15	20	31	39	45	46	48	48	48	48	51	51	50	48	47	41
London	13	14	18	19	20	21	24	31	40	48	52	54	58	61	63	63	62	64	66	63	48
South East Coast	15	18	18	20	22	24	25	31	36	42	50	54	56	58	58	57	58	57	55	53	50
Northern Ireland	5	5	5	6	6	7	9	11	13	13	15	20	22	21	21	21	22	22	22	22	22
Scotland	10	11	12	12	14	17	19	24	28	38	48	61	71	71	73	71	72	69	70	70	69
Wales	16	16	17	17	19	22	25	31	38	42	45	56	60	61	61	62	64	65	66	65	63
Total	*183*	*190*	*203*	*213*	*240*	*272*	*312*	*371*	*429*	*485*	*530*	*571*	*596*	*597*	*597*	*588*	*575*	*556*	*537*	*499*	*433*