Evaluation of the Utilisation and Safety of Gabapentinoids Prescribed in Primary Care in the United Kingdom

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List of Abbreviations

Abbreviation	Meaning
A&E	Accident & Emergency
ACMD	Advisory Council on the Misuse of Drugs
AEF	Adverse Events related to Falls
aHR	adjusted Hazard Ratio
AIDS	Acquired Immune Deficiency Syndrome
aIRR	adjusted Incidence Rate Ratio
APC	Admitted Patient Care
ATC	Anatomical Therapeutic Chemical
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BNF	British National Formulary
BSA	Business Service Authority
CCG	Clinical Commissioning Group
CCI	Charlson Comorbidity Index
CDC	Centres for Disease Control and Prevention
CDSS	Clinical Decision Support System
CE	Coefficient
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNCP	Chronic Non-Cancer Pain
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
DDD	Defined Daily Dose
DW	Durbin Watson
EHR	Electronic Health Record
EPD	English Prescribing Dataset
EU	European Union
FDA	Food and Drug Administration
FRD	Fracture-Related Drugs
GABA	γ-aminobutyric acid
GBTM	Group-Based Trajectory Model
GP	General Practitioner

GPN	Gabapentinoid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HES	Hospital Episode Statistics
HR	Hazard Ratio
IASP	International Association for the Study of Pain
IBM	International Business Machines
ICD-10	International Classification of Diseases, Tenth Revision
ID	Identification
IMD	Index of Multiple Deprivation
IQR	Inter Quartile Range
IR	Incidence Rate
IRR	Incidence Rate Ratio
ISAC	Independent Scientific Advisory Committee
ITSA	Interrupted Time-Series Aanalysis
ITT	Intention-To-Treat
LSD	Lysergic Acid Diethylamide
LSHTM	The London School of Hygiene & Tropical Medicine
LSOA	Lower-layer Super Output Areas
MAOI	Monoamine Oxidase Inhibitor
MD	Mean Difference
MEPS	Medical Expenditure Panel Survey
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
NPSAD	National Programme on Substance Abuse Deaths
OLS	Ordinary Least Squares
ONS	Office for National Statistics
OR	Odds Ratio
PHN	Post-herpetic neuralgia
QOF	Quality and Outcomes Framework
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
RR	Risk Ratio
SCCS	Self-Controlled Case-Series

SD	Standard Deviation
SMD	Standard Mean Difference
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
SNRI	Serotonin-Noradrenaline Re-uptake Inhibitors
SSRI	Selective Serotonin Re-uptake inhibitors
TCA	Tricyclic Antidepressants
THIN	The Health Improvement Network
TTE	Time-To-Event
UK	United Kingdom
US	United States
USA	Unites States of America
UTS	Up To Standard
WHO	World Health Organisation

Abstract

Introduction

Gabapentinoids were classified as controlled drugs in the United Kingdom (UK) in 2019 due to concerns about misuse and abuse, but their utilisation patterns and potential harms had not been investigated. This PhD project evaluates gabapentinoid utilisations and safety issues in users with chronic non-cancer pain (CNCP) and provides information for future interventions in England.

Methods

Practice-level prescribing data in England was used in two studies: (1) an ecological study identifying gabapentinoid prescribing trajectories and geographical variations in English general practices; (2) an interrupted time-series analysis testing the impact of the 2019 classification on the prescribing of gabapentinoids. A patient-level primary care database, the Clinical Practice Research Datalink, was used in four studies, all with study periods of 2005-2019: (1) a matched cohort study identifying user characteristics and risk factors for initiating gabapentinoids; (2) another matched cohort study investigating the risk of serious adverse events in gabapentinoids; (3) a cohort study identifying gabapentinoid utilisation patterns and their associated risks; and (4) a self-controlled case-series study investigating the risk of fracture hospitalisations in different periods during gabapentinoid exposure.

Results

Gabapentinoid utilisation increased in England from 2013. The general practice group with the highest level and the greatest increase in prescribing gabapentinoids from 2013-2019 was mainly located in the north of England. The classification significantly reduced the gabapentinoid prescribing level (β_2: -25.23; 95% CI: -38.78, -11.69) and trend (β_3: -1.89; 95% CI: -2.67, -1.12). Gabapentinoid users with CNCP have an increased risk of fracture hospitalisations (aHR: 1.11, 95% CI: 1.09, 1.13), suicide hospitalisations (aHR: 1.86, 95% CI: 1.80, 1.91), suicide deaths (aHR: 2.35, 95% CI: 2.15, 2.56), and drug-related deaths (aHR: 3.70, 95% CI: 3.29, 4.16) than non-users. High-dose gabapentinoid users have a significantly higher risk of fracture hospitalisation (aHR: 1.11, 95% CI: 1.05, 1.17), suicide hospitalisation (aHR: 1.07, 95% CI: 1.00, 1.15), suicide death (aHR: 1.29, 95% CI: 1.12, 1.49), and drug-related death (aHR: 1.40, 95% CI: 1.20, 1.63) than non-high-dose users. A higher risk of fracture hospitalisation occurs in the first two weeks of gabapentinoid exposure compared to the baseline non-exposure period (week 1 aIRR: 1.36, 95% CI: 1.24, 1.50; week 2 aIRR: 1.13, 95% CI: 1.01, 1.25).

Conclusion

Gabapentinoids are associated with an increased risk of serious adverse events in patients with CNCP, particularly for high-dose gabapentinoid exposure (i.e. supratherapeutic dosing). The highest risk of fracture hospitalisation occurs in the first week of gabapentinoid exposure. Risk factors and high-risk periods of serious adverse events in gabapentinoids can be considered at prescription to help reduce harm by disseminating these risks to clinicians and pharmacists and implementing them in clinical decision support systems. Gabapentinoid classification reduced the rate of increase of gabapentinoid prescribing in English primary care, especially in practices with the highest prescribing rates, so future regional policies could be effective in preventing gabapentinoid harm.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright statement

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Publications and awards

Peer-reviewed academic papers

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2. Xinchun Gu, Teng-Chou Chen, Ting-Li Su, Douglas Steinke, Li-Chia Chen. 2021. Investigating the prescribing trajectory and geographical drug utilisation patterns of gabapentinoids in primary care in England: an ecological study. *British Journal of Clinical Pharmacology*, 87(10), pp.4001-4012

Peer-reviewed conference presentations

1. Xinchun Gu, Teng-Chou Chen, Douglas Steinke, Li-Chia Chen. The characteristics of gabapentinoid users with chronic non-cancer pain in the primary care of United Kingdom. Oral presentation. The 38th Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management, 24-28 August 2022. Copenhagen, Demark. Pharmacoepidmiology and Drug Safety, 2022, 31: 46. (doi: 10.1002/pds.5518)
2. Xinchun Gu, Teng-Chou Chen, Douglas Steinke, Li-Chia Chen. Investigating the risk of severe adverse events in gabapentinoid users with chronic non-cancer pain in English primary care. Oral presentation. Prescribing and Research in Medicines Management (PRIMM UK & Ireland) 33rd Annual Scientific Meeting, 10 June 2022 at Holiday Inn Manchester City Centre, Manchester, UK.
3. Xinchun Gu, Teng-Chou Chen, Douglas Steinke, Li-Chia Chen. Classification of Gabapentinoid as Controlled Drug Reduced Gabapentinoid Prescriptions in Primary Care in England. Poster presentation. The 37th Annual International Conference on Real Evidence for the Real World (All Access), 23-25 August 2021 online. Pharmacoepidmiology and Drug Safety, 2021, 30: 168. (doi: 10.1002/pds.5305)
4. Xinchun Gu, Laura Hayward, Teng-Chou Chen, Douglas Steinke, Li-Chia Chen. Prescribing Trend and Factors Associated with Prescribing Benzodiazepines in Primary Care in England, 2013-2019. Poster presentation. The 36th Annual International Conference on Pharmacoepidemiology and Therapeutic Risk

Management (All Access), 16-17 September 2020 online. Pharmacoepidmiology and Drug Safety, 2020, 29:265. (doi: 10.1002/pds.5114)

5. Xinchun Gu, Tehreem Ahmed, Teng-Chou Chen, Douglas Steinke, Li-Chia Chen. Trend and Contributing Factors of Prescribing Antidepressants in Primary Care in England: 2013-2019. Poster presentation. The 36th Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management (All Access), 16-17 September 2020 online. Pharmacoepidmiology and Drug Safety, 2020, 29:261. (doi: 10.1002/pds.5114)
6. Xinchun Gu, Teng-Chou Chen, Douglas Steinke, Li-Chia Chen. 'Geographical Variation & Factors Associated with Prescribing of Gabapentinoids in England. Oral presentation. Prescribing and Research in Medicines Management (PRIMM UK & Ireland) 31st Annual Scientific Meeting, 17 January 2020 at the Spinningfields Conference Centre, Manchester, UK.
7. Xinchun Gu, Teng-Chou Chen, Douglas Steinke, Li-Chia Chen. Regional variation and increasing gabapentinoids prescribing in England. Poster presentation. The 35th Annual International Conference on Pharmacoepidemiology and Therapeutic Risk Management, 26-28 August 2019 at the Pennsylvania Convention Center, Philadelphia USA. Pharmacoepidmiology and Drug Safety, 2019,28(S2):278-279 (doi: 10.1002/pds.4864)

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Chapter 1. Introduction

1.1. Background

Chronic pain is defined as “persistent or recurrent pain lasting longer than 3 months” by the International Association for the Study of Pain (IASP) [1]. It has a high prevalence of around 45% in the United Kingdom (UK) [2, 3], which poses a large burden on patients and the UK health service system [4]. Therefore, optimising pain management and prioritising harm prevention strategies are crucial to reducing the burden of chronic pain in both patients and society.

Drug therapy is an important part of chronic pain management [5], where gabapentinoids had been the increasing first choice for pain management in recent years [6]. Gabapentinoids, including gabapentin and pregabalin, are a category of drugs that bind selectively to the $a_2\delta$ protein in the central nervous system (CNS) [7]. They are mainly indicated for focal seizures and peripheral neuropathic pain [8]. Since gabapentin and pregabalin were launched in the UK in 1993 and 2004 respectively, the number of users and prescriptions of gabapentinoids has increased markedly and this later raised experts' concerns about the misuse and abuse [6, 9-11]. As a result of the concerns, gabapentinoids were classified as controlled drugs in the UK to prevent potential misuse and abuse in April 2019, [12, 13]. However, current evidence for gabapentinoid-related harms was mainly from pharmacological and post-mortem studies [14, 15]. Although the British National Formulary (BNF) warned of gabapentinoids’ risk of abuse and dependence and severe respiratory depression, few epidemiological studies supported these statements at the population level.

Unlike pharmacological and post-mortem studies, epidemiological studies can help understand the drug utilisation patterns of gabapentinoids in real-world patients and investigate how they affect drug safety. They can, therefore, inform clinicians, policymakers and patients with recommendations in drug utilisation to actively prevent future harms from gabapentinoids. Therefore, this PhD project applied an epidemiological approach to investigate the drug safety issues relevant to the use of gabapentinoids so as to fill the population-level evidence gap in gabapentinoids' safety and provide recommendations for interventions. It was hypothesised that (1) geographical areas in England could have different gabapentinoid prescribing trends and respond differently to national prescribing policies; (2) gabapentinoids prescribed to patients with chronic non-cancer pain (CNCP) in the UK primary care settings could lead to an increased risk of drug-related deaths, suicides and fracture hospitalisations due to its pharmacological mechanism on the CNS [16]; (3) different utilisation patterns of gabapentinoids could contribute differently to the increased risk of drug-related death, suicide and fracture hospitalisation of gabapentinoids; (4) the risk of adverse events varies in different time periods during gabapentinoid exposure.

Pharmacoepidemiology is the study of "interactions between drugs and human populations" [17]. It applies the concept of epidemiology, "the study of distribution and determinants of health-related states and events in specified populations, and the application of this study to the control of health problems" [18] to study drug-related outcomes, mainly the adverse consequences. Therefore, when designing a pharmacoepidemiological study, it is important to be clear in specifying: (1) the events of concern, (2) the target population and (3) the application of the study results.

Some epidemiological studies on gabapentinoid use identified controversial risks of suicide [19, 20], increased risk of injury [21] and higher risk of opioid-related deaths when combined with opioids [22, 23]. However, they did not study the impact of gabapentinoid utilisation patterns or only studied the effect of gabapentinoids as add-on drugs. Also, none of the above epidemiological studies were conducted on the UK population. Therefore, the events of concern in this study were defined as serious adverse events including drug-related deaths, suicide death, suicide hospitalisation and fracture hospitalisation associated with gabapentinoids.

Although gabapentinoids were indicated for several diseases, their use in chronic pain needs the most attention because: (1) chronic pain has a high prevalence rate, (2) a high proportion of off-label gabapentinoid prescriptions were prescribed for chronic pain in the UK and (3) the long-term drug management for chronic pain indicates a longer time under risk [3, 6, 24]. Since cancer pain is a complicated condition that priorities quality of life [3], it was excluded from the chronic pain study population to avoid excessive confounding. Therefore, the target population of this project was the gabapentinoid user population with chronic non-cancer pain (CNCP), with a focus on those who experienced drug safety issues.

The evidence derived from this project is expected to inform policymakers about the effectiveness of implementing the gabapentinoid classification policy and identify regions that may need further local interventions. It could inform clinical guidelines and clinicians about the risks of gabapentinoids and optimise prescribing gabapentinoids to prevent harm. These together could help mitigate the risks associated with gabapentinoid prescriptions and improve patient safety.

1.2. Aim and objectives

This PhD project aims to evaluate the drug safety issues in gabapentinoid users with CNCP and support interventions on gabapentinoid utilisation in English primary care. The objectives of this project are:

(1) To evaluate the practice-level prescribing trend and its geographical variation and identify factors related to prescribing gabapentinoids in English primary care,
(2) To evaluate the impact of the April 2019 gabapentinoid classification on the practice-level prescribing of gabapentinoids and other pain-related drugs,
(3) To identify baseline characteristics of gabapentinoid users and risk factors for gabapentinoid initiation in patients with CNCP,
(4) To investigate the incidence rates and hazard ratios of serious adverse events in gabapentinoid users compared to gabapentinoid non-users in the CNCP population,
(5) To identify gabapentinoid utilisation patterns and investigate their association with serious adverse events in the CNCP population,
(6) To investigate the association between the time periods in gabapentinoid exposures and the risk of fracture hospitalisations.

1.3. Project outline

This PhD project includes six individual studies that research the safety of gabapentinoids at the practice and patient level (Figure 1-1) to support drug utilisation strategy. The study started with a literature review to identify evidence gaps in the safety of gabapentinoids. Then two studies using practice-level data were conducted to identify potential problems in the national prescribing trend of gabapentinoids and test the efficacy of the gabapentinoid classification policy to inform future policies and identify safety issues that need patient-level interventions. Based on the findings from the practice-level data, four studies using patient-level

data were conducted to investigate the risk of serious adverse events in gabapentinoid users and provide recommendations for practice and patient-level interventions to prevent harm. The chapter overview and the link between chapters are summarised below.

Chapter 2: Literature review

Chapter 2 summarises evidence on pharmacological therapies for chronic pain and the pharmacological and clinical perspectives on gabapentinoids' safety to inform the aim and objectives of this PhD project. This chapter also summarises and critiques available epidemiological studies that investigated the use of gabapentinoids to identify evidence gaps and form study questions.

Chapter 3: The prescribing trajectory and geographical drug utilisation patterns of gabapentinoids in English primary care

Chapter 3 is an ecological study analysing the prescribing trajectories and geographical variations in practice-level gabapentinoids prescribing. The study identifies an increase in gabapentinoids prescribing between 2013 and 2019, and a continuous increase in prescribing gabapentinoids in general practices located in northern England. This chapter reveals the potential of gabapentinoid misuse and abuse by identifying the high-prescribing general practices and also provides information for future practice-level interventions to prevent gabapentinoid-related harms.

Chapter 4: The impacts of gabapentinoid classification on the prescribing of gabapentinoids and pain-related medicines in English primary care

Chapter 4 is a quasi-experimental study evaluating the effect of the classification of gabapentinoids in April 2019 on the prescribing of gabapentinoids and other pain-related drugs using the same practice-level prescribing data as Chapter 3. This

study measures the effectiveness of implementing a national controlled drug policy on gabapentinoids and explores factors influencing the policy's effectiveness, which could inform further interventions where necessary.

Chapter 5: Data source and cohort identification

Chapter 5 is a methodology chapter that describes the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases and the development of the cohort and outcome identification code lists to prepare for the subsequent patient-level studies (Chapters 6-9). This chapter also describes the identification process of the CNCP study population from the CPRD database that is repeatedly referred to in the following studies and outlines the study cohorts in the following studies.

Chapter 6: Baseline characteristics associated with gabapentinoid initiation in patients with chronic non-cancer pain in English primary care

Chapter 6 is a matched cohort study identifying the baseline characteristics of gabapentinoid users and non-users in patients with CNCP and analysing them against the initiation of gabapentinoids using the CPRD data. This chapter applies a logistic regression analysis to identify the baseline characteristics related to gabapentinoid initiation. It also prepares the identification process for baseline characteristics in gabapentinoid users for the following studies as covariates.

Chapter 7. The risk of serious adverse events in gabapentinoid users and non-users with chronic non-cancer pain in English primary care

Chapter 7 is a matched cohort study assessing the risk of drug-related deaths, suicides and fracture hospitalisations in gabapentinoid users compared with non-users in CPRD-HES and CPRD-ONS linked data. This chapter adopts nonparametric (Kaplan-Meier analysis) and semi-parametric survival analyses (Cox

proportional hazard model and cause-specific proportional hazard model) to evaluate the risk of serious adverse events in gabapentinoid users and non-users.

Chapter 8: Gabapentinoid utilisation patterns and their association with serious adverse events in patients with chronic non-cancer pain in English primary care

Chapter 8 is a cohort study of gabapentinoid users with CNCP in CPRD-HES and CPRD-ONS linked data that expands upon the findings of Chapter 7 by evaluating the association between gabapentinoid utilisation patterns and the risk of serious adverse events. It identifies the persistent use, high-dose use and concurrent use of gabapentinoids, applies a drug survival analysis to study persistent gabapentinoid use, and adopts a Cox proportional hazard model with time-varying factors to investigate the association between high-dose gabapentinoid use and serious adverse events.

Chapter 9: The risk of fracture hospitalisations in gabapentinoid exposure periods in patients with chronic non-cancer pain in English primary care

Chapter 9 is a self-controlled case-series study of gabapentinoid users who experienced fracture hospitalisation in CPRD-HES data that compares the incidence of fracture hospitalisation in gabapentinoid exposure periods to non-exposure periods. Gabapentinoid exposure periods were split into 1-7 days, 8-14 days, 15-28 days, and 29+ days to evaluate the different risks of fracture hospitalisation over the exposure.

Chapter 10: Discussion and implications

Chapter 10 summarises the findings of the six studies and discusses the strength and limitations of the study designs to help interpret the findings appropriately. This chapter also provides implications from patient, clinician and policymaker

perspectives to optimise the utilisation of gabapentinoids in patients with CNCP and reduce harm.

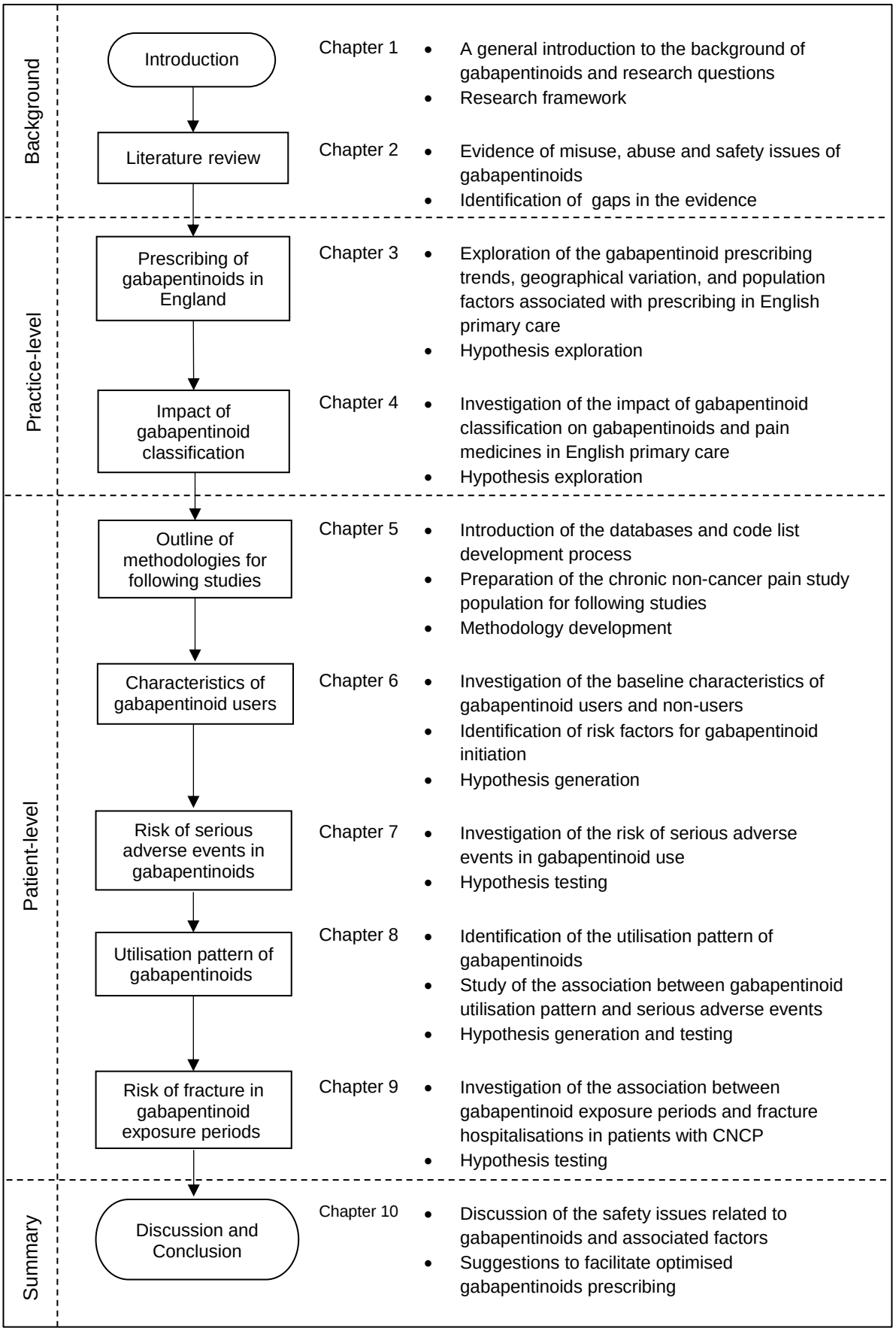


Figure 1-1. Conceptual framework and thesis development process

Chapter 2. Literature review

2.1. Introduction

This literature review aims to identify evidence gaps in the safety of gabapentinoids for chronic pain management, and to inform further studies. It begins with a review of the chronic pain prevalence in the UK and globally, which highlights the need for pain management to reduce the burden of chronic pain on patients and society. Then, the pharmacological and non-pharmacological pain management choices that are recommended in guidelines are summarised, so as to assess the position of gabapentinoids in chronic pain management. After that, gabapentinoids' pharmacology, licensed indications and efficacy for chronic pain are reviewed to enhance the understanding of gabapentinoids' position in chronic pain management. The control drug policies and utilisation of gabapentinoids in the UK and globally are reviewed, identifying a rapidly increasing trend of gabapentinoid prescribing. Finally, safety issues including adverse events and misuse and abuse of gabapentinoids are summarised to identify the gaps in epidemiological evidence about the safety of gabapentinoids for chronic pain management.

2.2. Chronic pain

2.2.1. Definition of chronic pain

Pain is defined as "a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components."[25]. It is a complicated physiological process and is sometimes difficult to classify. Today, pain is often categorised by its duration, aetiology, or physiology. A common classification is to divide pain by aetiology into nociceptive, inflammatory, and pathological pain [26]. Neuropathic pain and nociplastic pain are components of pathological pain that arise from altered functions within pain-related sensory

pathways [27]. When deciding on treatment strategies, pain is often divided into acute and chronic pain, then further categorised into a certain category of pain (cancer pain, neuropathic pain, low back pain, pain in older people, etc) [1].

Acute pain (e.g. postoperative pain) is the initiation phase of extensive, persistent nociceptive pain. The mechanism for acute pain can be viewed as tissue injury or damage triggering a physiological cascade. Although recovery from acute pain usually occurs within several weeks, it can sometimes progress to chronic pain if not well suppressed [28], which complicates the mechanism and treatment [29]. The International Association for the Study of Pain (IASP) defines chronic pain as "persistent or recurrent pain lasting longer than 3 months" [1, 30]. IASP's definition of chronic pain was adopted in this project to define patients with CNCP.

2.2.2. Prevalence of chronic pain

Chronic pain has had a high prevalence rate across the world for the last century. A literature review analysed 29 prevalence studies published in European countries between 2009 and 2011 and estimated an average chronic pain prevalence of 27% in the general adult population in Europe [31]. The 2016 United States (US) National Health Interview Survey reported an estimated chronic pain prevalence of 20.4% in adults, with 8.0% of US adults having high-impact chronic pain (i.e., interfering with work or life on most days or every day) [32]. Chronic pain has a concerning high prevalence in developing countries. A systematic review reported 34% (95% Confidence Interval (CI): 26-42%) of the general adult population in low- and middle-income countries have unspecified chronic pain, and the rate was much higher in the elderly populations (62%, 95% CI: 41-81%), but the studies reviewed had significant heterogeneity [33]. The prevalence rate of chronic pain varies between studies, even in the same region for a similar time period [34]. The reasons

could be due to variations in the definition of chronic pain, the sampling criteria of the study population (i.e. samples not representing the general population), and the adjustment of the prevalence rate (i.e. adjusting for demographic characteristics like age, sex, and income). Thus, the available prevalence data should be considered with care.

In the UK, chronic pain has a high prevalence rate. According to a self-completion questionnaire survey conducted in a UK community in 1999, about 50.4% of the 5,036 participants who were over 25 years old reported experiencing chronic pain, which is equivalent to 46.5% in the general population [2]. A systematic review published in 2016 synthesised pooled prevalence data from 7 studies representing 139,933 adult residents of the UK and reported the prevalence rate of chronic pain ranged from 35.0% to 51.3% [3]. A more recent cross-sectional study based on the Health Survey for England 2011 mapped chronic pain prevalence in regional and local authorities in England and suggested an overall prevalence of over 35%, with the highest prevalence in the North East and lowest in London (43.1% vs 29.0%) [35]. The high prevalence of chronic pain in the UK indicates the importance of a good pain management strategy to reduce the burden on patients and society.

2.2.3. The burden of chronic pain

The burden of chronic pain on society is substantial. According to the US Burden of Disease Collaborators estimation for years lost to disability caused by diseases in 2010, chronic pain conditions constituted three out of the four leading diseases (low back pain, musculoskeletal disorders, and neck pain) [36]. The economic burden caused by chronic pain is estimated to be high in many countries. The Institute of Medicine reported that chronic pain affects 116 million American adults, and the medical and lost productivity costs are between US$560 and US$635 billion every

year [37]. In Australia, the mean annual cost of chronic pain is estimated to be AU$ 22,588–$42,979 per patient [36], inclusive of non-financial costs. The mean healthcare costs for fibromyalgia in Spain are estimated to be €3,245.8 per patient per year [38] and for low back pain in Germany the figure is €1,322 per patient per year [39]. Although the disease burden of chronic pain has not been estimated in the UK, the high prevalence of chronic pain in the UK suggests that the disease burden is high.

On the patient side, chronic pain is a daily challenge that leaves the patients "disbelieved, stigmatised for not getting better or judged as not coping" [40]. Patients with chronic pain experience absence from work and unemployment due to chronic pain [31]. Patients suffering from chronic pain were found to easily sense the burden brought by them onto others (self-perceived burden), especially their families [41]. They are likely to live with poor mental health and self-esteem, experience breakdowns of relationships, and have socioeconomic disadvantages [40].

In addition, chronic pain has been found to be associated with some serious but seemingly disconnected outcomes. Patients experiencing chronic pain have an elevated risk of suicide [42]. It is widely accepted that depression is a common reason for suicide. To investigate the risk of depression in patients with chronic pain conditions, Gerrits *et al.* (2014) conducted a trial which excluded participants with a history diagnosis of depression or anxiety [43]. After 4 years' of follow-up, 15.5% of the participants had gained their first diagnosis of depression [43]. The risk of depression was associated with the severity of pain [43].

2.3. Management of chronic pain

Since chronic pain has a high prevalence, and treatment is complex and long-term, medical organisations and associations across the world have published a variety of guidelines to help improve the clinical management of chronic pain. The currently available guidelines for chronic pain treatment in the UK are *"Neuropathic pain in adults: pharmacological management in non-specialist settings"* and *"Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain"* published by the National Institute for Health and Care Excellence (NICE) [5, 44] and "*Management of chronic pain*" published by the Scottish Intercollegiate Guidelines Network [45]. These guidelines categorise the management of chronic pain into pharmacological and non-pharmacological sections, which both have advantages and disadvantages, and should therefore be considered based on patients' needs.

2.3.1. Non-pharmacological chronic pain management

Psychological therapy

Since early last century, there have been studies that support the concept that psychological factors play an important role in chronic pain, and this has now grown into a developed framework [46]. Psychological therapy has become an important component of multidisciplinary chronic pain management. There are several psychological interventions commonly used in chronic pain, such as self-regulatory, behavioural, cognitive-behavioural, and acceptance and commitment interventions [47]. A Cochrane systematic review suggested that evidence is insufficient for behavioural therapy, but cognitive behaviour treatment has demonstrated small positive effects on immediate outcomes [48].

Interventional therapy

Interventional procedures are commonly used in chronic pain management. Today, interventional procedures are usually categorised into injection therapy, surgical intervention and implantable devices [49]. However, although interventional therapies are widely used to relieve pain, there is a lack of evidence to support their efficacy because prospective randomised controlled trials are difficult to conduct for these therapies.

Other therapy

Common physical therapies for chronic non-cancer pain include manual therapy, exercise, and traction. Complementary and alternative therapies recommended for chronic pain include acupuncture, herbal medicine, and dietary therapies [45].

2.3.2. Pharmacological chronic pain management

Drug therapy is an important part of chronic pain treatment and has a long history. Although the World Health Organisation (WHO) “analgesic ladder” was first developed for cancer pain in 1986, it is now widely used to support the choice of painkillers for all types of pain [50]. It suggests that patients should promptly start oral drug therapy when pain occurs, and climb from the bottom of the analgesic ladder to the top [50]. The ladder starts with non-opioids such as aspirin and paracetamol, and then escalates to mild opioids (codeine), and finishes with strong opioids such as morphine. Sometimes other drugs are also added to help reduce any fear or anxiety derived from pain. Below are the major categories of drugs commonly used for chronic pain treatment.

Opioids

Opioids have a long history as pain-relieving drugs, but the American Centres for Disease Control and Prevention (CDC) emphasised the importance of starting pain control from non-opioid therapy in its guidelines for prescribing opioids for chronic pain in 2016 [51]. The evidence for the efficacy of opioids for treating chronic pain is not sufficient, and only supports short-term opioid use. According to a literature review conducted in 2008 [52], evidence from randomised controlled trials (RCTs) demonstrated that neuropathic pain does respond to opioids. A systematic review of RCTs evaluated the short-term efficacy of opioids, finding they decrease pain intensity by at least 30% for both neuropathic and musculoskeletal pain. However, this review failed to provide evidence for long-term efficacy due to the congenital time limitation in RCTs [53].

There are several observational studies evaluating the long-term efficacy of opioids for chronic pain, but most of them were conducted before the year 2000 and did not use functional or quality of life (QoL) improvement as outcomes, meaning these studies are insufficient evidence to support the long-term benefits of opioids. Long-term opioid use is commonly related to concerns about tolerance, and may lead to dose escalation and adverse events such as abnormal pain sensitivity, negative hormonal effects, and immunosuppression [54]. Moreover, there are growing concerns about opioid overdose and addiction. A cohort study analysed 9,940 opioid users from Washington and found those receiving higher doses of prescribed opioids are at increased risk of overdose [55]. The prevalence of opioid dependence in non-malignant chronic pain patients varies from 24% to 27.4% in different studies [56].

Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol

NSAIDs are commonly used to treat mild to moderate pain. Its mechanism in pain relieving is related to its effects on the cyclooxygenase (COX) enzyme which inhibits prostaglandin [57]. Available evidence only supports NSAIDs' use for low back pain and osteoarthritis knee pain. A recent Cochrane systematic review analysed 13 RCTs and confirmed NSAIDs' efficacy for chronic low back pain. The results suggest that NSAIDs are more effective at reducing pain intensity when compared with placebo, with no difference between non-selective and COX-2 selective NSAIDs [58]. Another systematic review supported NSAIDs providing short-term pain relief in patients with osteoarthritis in the knee [59]. In addition, NSAIDs were found to be used frequently for neuropathic pain, though there is currently insufficient evidence for their efficacy [60].

Paracetamol, like NSAIDs, is a popular over-the-counter painkiller, but there is insufficient evidence to support its efficacy for general chronic pain [61]. A Cochrane systematic review which involved 15 RCTs suggested that paracetamol significantly reduces osteoarthritis pain compared to placebo (standard mean difference, SMD -0.13, 95% CI -0.22 to -0.04), though the clinical usefulness is limited. The study also found paracetamol to be inferior to NSAIDs for relieving osteoarthritis pain, with no significant difference in safety outcomes [62].

Antidepressant drugs

Antidepressant drugs are divided by neurotransmitter reuptake specificity into several categories: the tricyclic antidepressants (TCAs), the serotonin-norepinephrine reuptake inhibitors (SNRIs), the selective serotine re-uptake inhibitors (SSRIs), the norepinephrine-dopamine reuptake inhibitors, the monoamine oxidase inhibitors (MAOIs), and others. Their mechanisms in inhibiting

pain are diverse but mostly related to the regulation of the neurotransmitters serotonin (5-hydroxytryptamine, 5-HT), and norepinephrine (NE). They also have impacts on many other pathways such as the dorsolateral prefrontal cortex, insular cortex, amygdala, and hippocampus [63].

The most commonly used categories of antidepressant drugs for chronic pain are TCAs, SNRIs, and SSRIs. Of these, TCAs are believed to be more effective than the other two categories because of their various effects at central and peripheral sites [64]. Antidepressants were found to be effective for treating central neuropathic pain, headaches, low back pain, fibromyalgia, and peripheral neuropathic pain (which includes post-herpetic neuralgia (PHN) and painful polyneuropathy) [64].

Anticonvulsant drugs

Anticonvulsants were first established for epilepsy, and were quickly adapted for use in pain management in the 1960s [65]. The precise mechanisms of anticonvulsants are still unclear, but there are several explanations such as modulation of voltage-gated calcium or sodium channels, enhancement of the γ-aminobutyric acid (GABA) inhibition, and stabilising effects on neuronal cell membranes [49, 65]. Anticonvulsants for pain management are mainly focused on neuropathic pain, though some are also effective for other chronic pain such as fibromyalgia. The reason anticonvulsants are effective for neuropathic pain probably involves the similarity between the pathophysiological and biochemical mechanisms observed in epilepsy and neuropathic pain [66]. The most frequently used anticonvulsant drugs for chronic pain are gabapentin, pregabalin, carbamazepine, and oxcarbazepine [49]. Gabapentin and pregabalin are recommended as first-line pharmacological therapies for neuropathic pain in the NICE guideline [44].

Other drugs

Benzodiazepines are indicated for short-term use for acute anxiety and insomnia but are popular among patients with painful symptoms, probably because anxiety and insomnia occur frequently in painful conditions [67, 68]. However, there is a lack of evidence on the efficacy of benzodiazepines for pain relief [67]. Topical agents are believed to provide the same pain relief as oral agents for local pain, but may need less dosage than oral agents and have fewer adverse events [69].

2.4. Gabapentinoids

2.4.1. Pharmacology of gabapentinoids

Gabapentin and pregabalin were originally designed as GABA analogues but were soon shown to have no obvious effect on $GABA_A$ and $GABA_B$ receptors, and no effect on GABA levels [70]. Later, they were found to bind to the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits of voltage-gated calcium channels. $\alpha_2\delta$-1 has been confirmed to be an important element related to the analgesic effects of gabapentinoids [70]. One possible hypothesis for the pain relief effect of gabapentinoids is the inhibition of calcium currents via high-voltage-activated channels may lead to a reduction in neurotransmitter release and attenuation of postsynaptic excitability [71]. However, the actual molecular mechanism of gabapentinoids in relieving pain remains unclear. Gabapentin and pregabalin share many pharmacokinetic and pharmacodynamic properties but differ in the absorption process [16]. In contrast to gabapentin's dose-dependent pharmacokinetics, pregabalin shows linear pharmacokinetics and no saturation of absorption. This is because gabapentin only has one transporter (the large neutral amino acid transporter 1), which is saturable, while pregabalin has this transporter and several others [72].

2.4.2. Indications for gabapentinoids

The number of gabapentinoids' indications increased gradually after they first came to market in 1993 for gabapentin and in 2004 for pregabalin [71]. Gabapentin was first approved as an adjunctive therapy for partial seizures under the brand name Neurontin by the US Food and Drug Administration (FDA) in 1993 and this indication was extended to children over 3 years old in 2000 [73]. The gabapentin once-daily tablet (Gralise) for the management of PHN and the gabapentin prodrug (Horizant) to treat restless leg syndrome and PHN in adults, were approved by the FDA in 2011 and 2012 respectively. In European Union (EU) countries, gabapentin is approved as an adjunctive treatment for focal seizures with or without secondary generalisation, monotherapy for focal seizures with or without secondary generalisation, peripheral neuropathic pain, migraine prophylaxis, and menopausal symptoms (particularly hot flushes) in women with breast cancer [74].

Following gabapentin, pregabalin (brand name Lyrica) came into the American market at the end of 2004 with approval for the management of neuropathic pain associated with diabetic peripheral neuropathy and post-herpatic neuralgia. Later, pregabalin received approval for partial seizures, fibromyalgia, and neuropathic pain associated with spinal cord injury in the US [75]. In EU countries, pregabalin is approved with indications for peripheral and central neuropathic pain, adjunctive therapy for focal seizures with or without secondary generalisation, and generalised anxiety disorder [74]. Although the indication for anxiety disorder is not approved for pregabalin in the United States of America (USA), there was sufficient evidence for it to be licensed for treating generalised anxiety in the EU [76].

Outside of the approved indications, many exploratory studies aiming to expand gabapentinoids' indications have also been published. Since the launch of gabapentin in 1993, clinical trials of gabapentin had been conducted for diseases such as bipolar disorder, trigeminal neuralgia, fibromyalgia, and other chronic pain syndromes [75, 77], but in each case failed to provide solid evidence for gabapentin treating the target disease. Similarly, a large number of clinical trials were carried out to test the effectiveness of pregabalin for various diseases, such as irritable bowel syndrome, acute anxiety, alcohol dependence, and itching [78]. These trials were exploratory, and most were not followed by confirmatory testing within five years, but they are likely to encourage the off-label prescribing of gabapentinoids by clinicians.

2.4.3. Efficacy of gabapentinoids for chronic pain

Many Cochrane systematic reviews of randomised controlled trials (RCTs) were conducted to evaluate the efficacy of gabapentinoids on chronic pain symptoms (Table 2-1). Results from 37 randomised controlled trials which compared gabapentin with a placebo showed that 32% of patients with peripheral neuropathic pain and 38% of patients with peripheral diabetic neuropathic pain achieved at least 30% pain relief after receiving gabapentin [79]. However, there was insufficient evidence to support gabapentin's superior to placebo in other neuropathic pain (37 RCTs; 5914 participants) and fibromyalgia (1 RCT; 150 participants) [79, 80]. Pregabalin was proven effective in reducing the pain intensity by at least 50% compared to placebo in over 30% of the participants with post-herpetic neuralgia and painful diabetic neuropathy (45 RCTs, 11,906 participants), mixed or unclassified post-traumatic neuropathic pain and fibromyalgia (5 RCTs, 3,283 participants), but there was inadequate RCT evidence to support its efficacy in central neuropathic pain [81-83].

In contrast to the studies suggesting gabapentinoids' effectiveness in many indications, non-superior results on the effectiveness of gabapentinoids compared with placebo have been published more frequently since 2015. A randomised controlled trial conducted on 209 patients in 2017 suggested that pregabalin did not reduce the intensity of leg pain associated with sciatica when compared with placebo (adjusted mean difference, 0.3; 95% CI -0.5 to 1.0; P=0.46) [84]. A systematic review argued that gabapentinoids showed a statistically significant but small improvement in pain relieving (i.e. not clinically relevant), which did not support the use of gabapentinoids in chronic low back pain [85].

There are limitations in the methodology of the majority of randomised controlled trials that evaluate pain relief, so the evidence on gabapentinoids' efficacy should be interpreted with caution. Firstly, most of the clinical trials use different pain scales to show the reduction of pain intensity, which may be biased in many steps of the procedure (patient's subjective feelings, patients' understanding of the questions in the scale). Secondly, some chronic pain may resolve over time without treatment (e.g. sciatica) [86], so the effect of analgesics may sometimes be enhanced by the natural process of pain in clinical trials and make the effect of analgesics overestimated. Thirdly, clinical trials typically involve short treatment periods. Chronic pain is a complex and multifaceted phenomenon that persists over extended periods, and clinical trials may not fully capture the long-term effects of pain medication. Pain conditions can be affected by many factors, including patient characteristics, pain types, comorbidities, etc. which can impact the measured effectiveness of treatments. Fourthly, clinical trials have the potential for selection bias. Typically, only patients who meet strict criteria can be included in each study, which can limit the generalizability of study results to broader populations. Different studies may also use different criteria, making cross-study comparisons difficult.

Table 2-1. Systematic reviews on the efficacy and safety of gabapentinoids

Author	Disease	RCTs	Patients	Intervention and Control	Main outcome
Wiffen, 2017 [79]	Neuropathic pain	37	5914	Gabapentin (1200 mg or more) vs placebo	A higher proportion of gabapentin users achieved at least 50% pain relief for patients with post-herpetic neuralgia (RR 1.8; 95% CI: 1.5 to 2.1) and painful diabetic neuropathy (RR 1.9; 95% CI: 1.5 to 2.3). Participants taking gabapentin experienced dizziness (19%), somnolence (14%), peripheral oedema (7%), and gait disturbance (14%).
Cooper, 2017 [80]	Fibromyalgia	1	150	Gabapentin vs placebo	38/75 (49%) in gabapentin and 23/75 (31%) in placebo achieved 30% or greater pain reduction when compared to the baseline pain condition. 16% in gabapentin and 9% in placebo discontinued because of adverse events.
Derry, 2019 [81]	Neuropathic pain	45	11,906	Pregabalin (150 mg, 300 mg and 600 mg) vs placebo	**Postherpetic neuralgia:** More participants had at least 50% pain intensity reduction with pregabalin (300 mg: 32% vs 13%, RR 2.5, 95% CI: 1.9 to 3.4; 600 mg: 41% vs 15%, RR 2.7, 95% CI: 2.0 to 3.5). Somnolence and dizziness were more common with pregabalin than with placebo (somnolence 300 mg 16% vs 5.5%, dizziness 300 mg 29% vs 8.1%). **Painful diabetic neuropathy:** More participants had at least 50% pain intensity reduction with pregabalin (300 mg: 31% vs 24%, RR 1.4, 95% CI: 1.01 to 1.2; 600 mg: 41% vs 28%; RR 1.4, 95% CI: 1.2 to 1.7). Somnolence and

					dizziness were more common with pregabalin than with placebo (somnolence 300 mg 11% vs 3.1%, dizziness 300 mg 13% vs 3.8%).
Derry, 2016 [82]	Fibromyalgia	5	3283	Pregabalin (150, 300, 450, or 600 mg daily) vs placebo	A higher number of pregabalin users achieved at least 50% pain intensity reduction (450 mg: RR 1.8, 95% CI: 1.4 to 2.1). Specific adverse events (dizziness, somnolence, weight gain and peripheral oedema) were more common with pregabalin than placebo.
Gurusamy, 2016 [83]	Pancreatic pain	1	64	Pregabalin (escalating dose) vs placebo	Short-term use (two weeks to three months) of pregabalin decreases short-term opiate use, and short-term pain scores, but increases the adverse events compared to placebo, in people with chronic pancreatitis.
Shanthanna, 2017 [85]	Chronic low back pain	8	-	Gabapentin vs. placebo	Gabapentin compared with placebo showed minimal improvement of pain (MD=0.22 units, 95% CI: -0.5 to 0.007, I^2=0, GRADE very low). Following adverse events were more commonly reported with gabapentin: dizziness (RR=1.99, 95% CI: 1.17 to 3.37, I^2=49); fatigue (RR=1.85, 95% CI: 1.12 to 3.05, I^2=0); difficulties with mentation (RR=3.34, 95% CI: 1.54 to 7.25, I^2=0); visual disturbances (RR = 5.72, 95% CI: 1.94 to 16.91, I^2=0).
				Pregabalin vs other analgesics	Pregabalin showed greater improvement in pain (MD=0.42 units, 95% CI: 0.20 to 0.64; I^2=0). Dizziness was more

	common compared to the active comparator (RR=2.70, 95% CI: 1.25 to 5.83).

Note: RCT: randomised controlled trial; RR: risk ratio; CI: confidence interval; MD: mean difference; GRADE: Grading of Recommendations Assessment, Development and Evaluation

2.4.4. Utilisation of gabapentinoids

Utilisation of gabapentinoids in the UK

Gabapentin and pregabalin were increasingly prescribed in the UK after their approval for neuropathic pain. The increasing utilisation of gabapentinoids is likely to be largely driven by the chronic non-cancer pain (CNCP) cohort. An epidemiological study published in 2018 found that the rate of patients initiating gabapentin or pregabalin in the CPRD database tripled between 2007 and 2017 in primary care in the UK [6]. Off-label use of gabapentinoids, which is defined as use for non-neuropathic pain or other uses not indicated for, was found in 50% of gabapentinoid users in 2017 [6]. This study identified that 20% of new gabapentinoids prescriptions coincided with an opioid prescription, and treatment of non-neuropathic pain accounted for most of the off-label prescriptions [6]. This indicates that gabapentinoids are frequently prescribed for chronic pain. Another study of patients with osteoarthritis in the CPRD found that the annual age-standardised incidence rate of first gabapentinoid prescriptions was 27.6 per 1000 person-years in 2015, compared with 1.6 in 2000 [87]. The incidence rate of first gabapentinoid prescriptions was higher for female and younger patients [87]. In Scotland, the annual rate of prescriptions between 2006 and 2016 increased 4-fold for gabapentin (from 164,630 to 694,293), and 16-fold for pregabalin (from 27,094 to 435,490) [88]. The same study, which used Scottish national data from the Information Service Division, found that 49.9% of gabapentinoid users are co-prescribed opioids and 26.8% are co-prescribed benzodiazepines [88]. It also found that gabapentinoid users who were prescribed three or more prescriptions in 2016 had a mean age of 58.1 years, were more likely to be female (62.5%), and were more likely to live in deprived areas in Scotland [88].

The characteristics of pregabalin users and the utilisation patterns of pregabalin were investigated in a study using the Health Improvement Network (THIN) database in the UK between 2004 and 2009 [89]. THIN is a primary care database holding electronic patient-level medical records for ~7.5 million patients from General Practitioner (GP) practices in the UK. The study identified 18,951 pregabalin users with a median age of 58 years and a gender makeup of 60.1% female [89]. The median of the prescribed daily dose of pregabalin was 150.0 mg/day for all users, but was higher for epilepsy (191.9 mg/day) and neuropathic pain (158.0 mg/day) [89]. It was also found that 18.4% of pregabalin users had a history of substance abuse [89].

Utilisation of gabapentinoids in other countries

In addition to the trend found in the UK, gabapentinoid utilisation was found to be increasing in many countries. Pregabalin had the 14th highest subsidisation (cost) of drugs subsidised by the Australian government in 2017-2018, where most of the drugs with higher costs were extremely expensive drugs for specific diseases (e.g. monoclonal antibodies for cancer) [90]. The large expense of pregabalin reflects the high utilisation of pregabalin in Australia. In Japan, the number of new pregabalin users increased from 2010 to 2013, but the initial and maximum daily doses decreased over the same period [91]. In the US, 64 million gabapentin prescriptions were dispensed in 2016, making it the 10th most commonly prescribed medication [73]. The proportion of gabapentinoid users among all adults in the US Medical Expenditure Panel Survey (MEPS) increased significantly from 1.2% in 2002 to 3.9% in 2015, with gabapentin making up the majority of prescriptions (82.6%, 95% CI: 81.0% to 84.2%) [92]. When breaking the trends down into gabapentin and pregabalin, the number of gabapentin users was stable before 2008, but started to increase after this, while the trend for pregabalin plateaued after 2008. An

increasing combination of gabapentinoids with opioids or benzodiazepines was also found in the same study [92].

A cohort study using US healthcare utilization data found that gabapentinoids were the most common initial drug therapy for fibromyalgia; more common than amitriptyline and duloxetine [93]. It was found that 40% of gabapentin initiators and 45% of pregabalin initiators remained on the treatment after three months, and ~30% of gabapentinoid users remained on the treatment after six months [93]. Pregabalin was found to be the second most commonly used medication for treating chronic low back pain (after non-steroidal anti-inflammatory drugs) according to an administrative claims database analysis in Japan between 2013 and 2017 [94].

Gabapentionid control policies

The utilisation of gabapentinoids is not comparable between countries because policy and licensed indications vary between countries. Gabapentinoids were classified as controlled C drugs in April 2019 in the UK [13], but only pregabalin is classified as a Schedule V controlled substance in the US (due to the potential of euphoria) [95]. There is currently no national policy on gabapentin in the US, while state policies vary. Gabapentin was classified as a Schedule-V medication in Kentucky and Tennessee in July 2017 and July 2018 respectively, which means the prescribing of gabapentin is limited to authorised practitioners [96]. Other states in the US have not classified gabapentin as a controlled drug, but eight states require a mandatory report of each gabapentin prescription to the Prescription Drug Monitoring Program [96]. Utilisation can also be influenced by insurance coverage. The utilisation of pregabalin increased significantly after a restriction on reimbursement for pregabalin was removed in 2013 in Ontario, Canada [97].

2.5. Safety concerns about gabapentinoids

2.5.1. Adverse events in gabapentinoids

Common side effects

The common side effects of gabapentin and pregabalin include dizziness, drowsiness, confusion, memory loss, diarrhoea, and vomiting [8]. An observational cohort study using the dispensed National Health Service (NHS) prescriptions database was conducted on 3,100 patients in the UK and found that drowsiness/sedation, dizziness, and malaise/lassitude were the most frequently reported adverse events during the first month of gabapentin treatment [98]. Other adverse reactions, such as a dry mouth, oedema, and blurred vision were also found to occur frequently during gabapentinoid use [74]. Gabapentinoids were found to be associated with fractures in patients over 50 years old (Odds Ratio (OR)=1.79, 95% CI = 1.59-6.92) in a case-control study conducted in Taiwan [99]. This seems to be related to the dizziness caused by gabapentinoids, as dizziness and somnolence are adverse events commonly seen in both gabapentin and pregabalin users [79-83, 100, 101].

Serious adverse events

No serious adverse events (e.g. death) were found in clinical trials that were designed to evaluate the efficacy of gabapentinoids. However, the British National Formulary (BNF) warned in 2017 that gabapentinoids were associated with a rare risk of severe respiratory depression, even without concomitant opioid medicines [74]. The Medicines and Healthcare products Regulatory Agency (MHRA) issued a warning in 2008 on the risk of suicidal thoughts and behaviour in users of antiepileptic drugs (including gabapentin and pregabalin) [74]. In April 2019, a new

warning about the potential for misuse and abuse was issued by the BNF, which particularly emphasised the interactions between gabapentinoids and opioids [74].

According to a systematic review of abuse and misuse of gabapentin and pregabalin, the majority of acute overdose cases involving gabapentinoids resulted in benign symptoms and most patients fully recovered after treatment [102]. This indicates a low risk of death for gabapentinoids alone. The cases with the highest acute ingestions of gabapentin (91,000 mg) and pregabalin (11,500 mg) both recovered after treatment. All fatal overdose cases involving gabapentinoids also involved other drugs [102].

Although overdosing on gabapentinoids alone may not directly lead to death, gabapentinoids have been increasingly detected in post-mortem studies. Pregabalin was detected in 4.4% of the 4,200 autopsies conducted at the institute of forensic medicine in Munich from October 2010 to September 2012 [103]. In the subgroup of cases attributed to drug-dependency, the rate of pregabalin detection rose from 5.5% (4 of 72 cases) in the first year to 29.8% (26 of 87 cases) in the second year. Opioids were identified in every pregabalin-positive drug-dependent individual, with fentanyl and methadone most frequently detected, followed by morphine, codeine, and 6-Monoacetylmorphine [103]. A study in Finland in 2010-2011 found that pregabalin poisoning accounted for 10.1% of deaths involving pregabalin, and gabapentin poisoning accounted for 4.7% of deaths involving gabapentin [104]. A post-mortem study in Scotland detected concentrations of pregabalin exceeding the reference concentration in 33% of all tested samples in the lab [105].

In the UK, the number of drug-related deaths involving gabapentin or pregabalin increased significantly from 12 in 2012 to 190 in 2017, according to the ONS [106]. In the 3,750 deceased samples reported by Coroners in London and South East

London from January 2016 to December 2017, gabapentin tested positive in 118 (3.1%) samples, and pregabalin tested positive in 229 (6.1%) samples. In the gabapentinoid-positive cohort, non-heroin opioids were the most common concomitant drugs [107]. Similarly, the proportion of substance abuse deaths that involved gabapentinoids increased from 8.9% in 2014 to 32.3% in 2020, according to the National Programme on Substance Abuse Deaths (NPSAD) [108]. Opioids were co-detected in 92.0% of the gabapentinoid-positive death cases [108]. Prevalence data for gabapentinoid-related deaths is only collected in post-mortem studies when gabapentinoids are tested for by a coroner to be documented in the death record. Therefore, the rate of gabapentinoid-related deaths may be underestimated in post-mortem studies [107].

The association between gabapentinoid exposure and death has been investigated in particular populations in epidemiological studies. A retrospective cohort study in a Swedish nationwide register database assessed the association between prescribing sedatives and mortality for patients in opioid maintenance treatment. Pregabalin prescriptions were found to be associated with overdose death (hazard ratio: 2.82, 95% CI: 1.79-4.43) [109]. A nested case-control study between 1997 and 2016 on Ontario residents who received prescriptions for opioids (n=1,417) found that concomitant exposure to pregabalin is associated with significantly increased odds of opioid-related death (adjusted OR 1.68, 95% CI: 1.19 to 2.36) compared to opioids alone [22]. Another case-control study conducted in the same Ontario setting found that gabapentin prescribed with opioids is associated with significantly increased odds of opioid-related death (adjusted OR 1.49, 95% CI: 1.18 to 1.88), compared to opioids prescribed alone [23].

Suicide is another serious adverse event relevant to gabapentinoids. In 2018, the FDA warned of an elevated risk of suicidal behaviour or ideation associated with the

use of antiepileptic drugs, including gabapentin and pregabalin, based on a meta-analysis of 11 drugs [110]. Patients who initiated an anticonvulsant between July 2001 and December 2006 were identified using the US HealthCore Integrated Research Database [111]. The risk of suicidal acts (non-fatal or fatal suicide attempts) is higher for gabapentin users (hazard ratio: 1.42, 95% CI: 1.11-1.80), especially in the subgroups of younger and older patients, patients with mood disorders, and patients with epilepsy or seizures [111]. A Swedish self-controlled study between 2006 and 2013 identified 10,026 (5.2%) suicides among patients that were prescribed gabapentinoids [20]. It found gabapentinoids are associated with an increased risk of suicidal behaviour and suicide death (age-adjusted Hazard Ratio (HR): 1.26, 95% CI: 1.20, 1.32) [20]. However, there is conflicting evidence on the association of gabapentin with the risk of suicide. A study from 2000-2006 identified gabapentin users and extracted their diagnoses from the US PHARMetrics Patient-Centric Database to assess the association between gabapentin use and suicide. The results showed that gabapentin does not increase the risk of suicide attempts in non-psychiatric populations, and may reduce the risk of suicide in the population with psychiatric disorders [19].

2.5.2. Potential of misuse and abuse

Pharmacology of gabapentinoid misuse and abuse

A potential mechanism of gabapentinoid abuse is the impact of gabapentinoids on the dopaminergic “reward” system, which is usually related to addictive drug liability [112]. As the absorption of pregabalin is faster than gabapentin it could lead to a higher blood concentration when abused, meaning the risk of abuse is likely to be higher for pregabalin [112].

Prevalence of gabapentinoid misuse and abuse

The prevalence of misuse and abuse of gabapentinoids in the general population is low. An online questionnaire survey conducted in the UK evaluated the abuse potential of baclofen, gabapentin, and pregabalin in 2013 [113]. The survey included 1,500 individuals and found the lifetime prevalence of misuse was 1.1% for gabapentin and 0.5% for pregabalin [113]. Similarly, a study using the French Pharmacovigilance Database between 2010 and 2015 found the potential of pregabalin-related abuse or dependence was lower than for clonazepam (only 1.5% of the drug abuse or/and dependence cases had pregabalin exposure) [114].

Nevertheless, the reported number of gabapentinoids misuse and abuse cases has increased in the past decade. From 2004 to 2015, increasing misuse, abuse and dependence of gabapentinoids was found in the European Medicines Agency's EudraVigilance database, which collects suspected adverse drug reactions for all medicinal products authorised in Europe [115]. The German Federal Institute for Drugs and Medical Devices drug adverse events database found that the proportion of reports of pregabalin abuse or possible dependence among all adverse events increased from 5% in 2008 to 24% in 2012. In the same study, the most significant risk factors were male sex and a history of polytoxicomania [116].

The abuse liability of pregabalin was demonstrated to be low when administered as single doses at 75 mg (within the maximum recommended daily dose) and 150 mg (supratherapeutic dose) in a double-blind randomized crossover study involving 16 healthy volunteers [117]. However, a dose-dependent effect of euphoria or feeling "high" was found for both gabapentin and pregabalin, especially when overdosed [118, 119]. In 2011 a qualitative study collected comments from websites/forums (e.g. the websites of online pharmacies) that may contain gabapentinoid users'

opinions, and found some gabapentinoid users reach euphoria by overdosing on gabapentinoids or administrating them via other routes such as intravenously or rectally [119] [120]. Some of the abusers prefer pregabalin because a smaller dose can achieve the same euphoric effect. The comments contain users' experiences with the extremely high tolerance level of both gabapentinoids. Some comments mentioned trying the combination of gabapentinoids with alcohol, prescribed drugs (benzodiazepines and zopiclone), illicit/recreational drugs (hashish/marijuana; heroin/opioids; amphetamines; Lysergic Acid Diethylamide (LSD)), and legal highs (mephedrone or 'meow meow') [120]. The above findings support the concern that gabapentinoid misuse and abuse are more likely to occur in specific populations (i.e. people with a substance misuse history or people using gabapentinoids combined with other drugs like opioids) than the general population.

Factors associated with gabapentinoid misuse and abuse

Patients with a history of substance abuse (e.g. cannabis, benzodiazepines, and heroin abuse) are at higher risk of abusing gabapentinoids [102]. In a systematic review aiming to assess the extent of gabapentinoid misuse and abuse, gabapentinoids were found to be frequently combined with opioids, alcohol, benzodiazepines, zopiclone, marijuana, amphetamines, lysergic acid diethylamide, baclofen, selective serotonin reuptake inhibitors, and quetiapine [102]. This review also found that current or past opioid abuse was the most significant factor associated with gabapentinoid abuse [102]. Non-prescribed gabapentinoids were found to be used by 22% of patients with substance misuse problems in Scottish substance misuse clinics [121], mainly to become intoxicated and enhance methadone effects.

The coexistence of opioid abuse and gabapentinoid misuse or abuse is frequently mentioned in the literature. The European Medicines Agency's EudraVigilance found that opioids were found to be the top combined drugs in cases of gabapentinoids misuse identified in the European Medicines Agency's EudraVigilance, followed by antidepressants and benzodiazepines [115]. Meanwhile, misuse of gabapentinoids was frequently found in the opioid use disorder population, some of which use gabapentin specifically to get "high" [122-125]. A questionnaire survey conducted on 250 patients registered in a community correctional centre who had substance use disorders aimed to specify the association between abuse of gabapentin and opioid use disorder [122]. Out of patients who had opioid use disorder, 26% endorsed gabapentin abuse. In contrast, only 4% of the patients who did not have opioid use disorder reported non-medical gabapentin abuse [122]. Similarly, among opioid users who received detoxification in the US, 22% had misused gabapentin and 7% misused pregabalin. In comparison, 10% of opioid users had misused clonidine and 11% had misused amphetamine salts [123]. In a study testing urine samples from opiate-addictive patients in Germany, 12.1% detected pregabalin, while none of the patients tested had an on-label indication for pregabalin [124].

2.6. Summary of literature review

The high prevalence of chronic pain ranging from 35.0% to 51.3% in the UK [3] suggests a high disease burden on both patients and society, as measured in countries with a similar prevalence rate. The high burden of chronic pain highlights the need for optimised pain management, which normally includes pharmacological and non-pharmacological therapies. Among the pharmacological therapies, gabapentinoids are an increasingly selected choice because of their efficacy in treating chronic pain compared to other medicines. However, gabapentinoid safety has not been fully studied.

An increasing prescribing trend of gabapentinoids was identified in the UK, but the available studies investigating gabapentinoid prescribing trends and geographical variations in England were either conducted in sampled databases which may not be representative of the national population or not adjusted for population over time which could bias the results [6, 87, 88]. Therefore, an ecological study assessing population-adjusted national prescribing trends and the geographical variations in gabapentinoid prescribing in England could validate the prescribing trend identified in other studies, and also identify the regional safety issues relevant to gabapentinoids. Also, the effect of the gabapentinoid classification policy which could inform further interventions to help reduce harm has not been researched.

Evidence gaps were found in the characteristics of gabapentinoid users and the influential factors for prescribing gabapentinoids in patients with chronic pain. Three studies identified the characteristics of gabapentinoid users in the UK, but none of them were conducted on gabapentinoid users with CNCP in English primary care [87-89]. Investigating the influential factors for prescribing gabapentinoids in patients with CNCP could highlight risk factors associated with a higher risk of adverse events.

Similarly, the drug utilisation patterns of gabapentinoids have not been fully studied. The only available study investigated the utilisation pattern of pregabalin in 2009 in the THIN database, which was only one year after pregabalin was approved in the UK, and is likely to be outdated [89]. Different gabapentinoid utilisation patterns could result in different pain relief efficacy, and also different adverse event risks. Moreover, the misuse and abuse potential of gabapentinoids was found to be high, but the risk of gabapentinoid misuse and abuse in primary care is unclear.

Therefore, the drug utilisation patterns of gabapentinoids in patients with CNCP are worth studying.

Although the common side effects of gabapentinoids are dizziness and drowsiness, and these are not a large problem for the general population, they can sometimes lead to serious outcomes in specific populations (e.g. falls and fractures in older people). However, the fracture risk has not been estimated for gabapentinoid users with CNCP in English primary care. A published study used a case-control study to evaluate the fracture risk in gabapentinoid users in Taiwan [99], which may have insufficient confounder adjustment. The risk of opioid-related death was found to be associated with gabapentinoid exposure in opioid users [22, 23], but the findings were limited to opioid users and opioid-related death, and the risk of drug-related death associated with gabapentinoids alone has not been estimated. The evidence of suicide risk in gabapentinoid users is conflicting, and no studies were conducted on the UK population. Therefore, evidence gaps were identified in the risk of fracture, drug-related death, and suicide associated with gabapentinoids in patients with CNCP. None of the available studies investigated the impact of gabapentinoid utilisation patterns on the risk of adverse events in patients with CNCP. Therefore, studies evaluating the risk of serious adverse events (i.e. fracture, drug-related death, and suicide) in gabapentinoid users with CNCP, and the effect of gabapentinoid utilisation patterns on the risks are needed.

Chapter 3. The prescribing trajectory and geographical drug utilisation patterns of gabapentinoids in English primary care

3.1. Introduction

Since 2013, a growing number of drug-related deaths involving gabapentinoids in England [11, 126, 127] raised concerns about gabapentinoid safety. This concern was cognate to the ‘opioid epidemic', the rapid growth in prescribing opioids resulted in an escalating number of opioid overdoses and deaths in the United States (US) [128]. Therefore, a similar increasing trend of prescribing gabapentinoids in the UK could be worrying as it could lead to more gabapentinoid-related harms. However, breaking the national gabapentinoid prescribing trend into particular general practices by their prescription pattern and mapping them to identify regions that need more attention could help manage the concern.

Several published drug utilisation studies using various data sources and study populations have attempted to quantify gabapentinoid prescribing in the UK. An ecological study analysed national prescribing data and found an increase in the number of prescriptions of gabapentinoids from 2013 to 2018 in England [9]. Another drug utilisation study of gabapentinoid users collected data from a UK primary care database, the Clinical Practice Research Datalink (CPRD), and found the number of patients newly prescribed gabapentinoids tripled from 2007 to 2017 [6]. However, none of the published studies investigated the national increasing trend of prescribing gabapentinoids using trajectory models or at the geographical level in English primary care.

The determinants of the increased gabapentinoid prescribing trend could help understand the increase and help identify potential harms. Evidence indicates that

patients' demographics and comorbidities are associated with prescribing gabapentinoids [89, 129]. Socioeconomic status, which was highly correlated with people's residential area, was found to be associated with prescribing for many medicines [130-134] and may also apply to gabapentinoid prescribing [9]. Socioeconomic status influences people's lifestyle, health status, level of access to health services, medication-taking behaviours and many other indirect pathways to health care [130]. Low socioeconomic status was associated with a higher risk of being prescribed an inappropriate medication in a French study [131]. It is hypothesised that practices in more deprived areas are associated with higher prescribing rates and increasing prescribing trends of gabapentinoids in England. One study did suggest an association between socioeconomic status and gabapentinoid utilisation in English primary care [9], but the methods used to quantify gabapentinoid utilisation and confounding adjustments limited the reliability of the results, so further work is required.

In England, socioeconomic status is highly correlated to the location of the household and geographical area [135]. Socioeconomic status in England is measured by the Index of Multiple Deprivation (IMD) which is a score weighted by seven domains relating to deprivation in Lower-Layer Super Output Areas (LSOAs, a geospatial unit used in England and Wales) level [135]. From April 2013 to July 2022, general practices in local geographical areas were grouped into Clinical Commissioning Groups (CCGs), which were responsible for planning, commissioning, and deciding priorities and strategies for local health care services, including medicine optimisation and deprescribing strategies [25]. Consequently, the CCG locality was also associated with medicine prescribing. Meanwhile, geographical variation of opioid, antibiotic and antidepressant utilisation [132, 134, 136] has been found in the UK.

3.2. Aim and objectives

This ecological study aims to investigate the long-term prescribing trajectory of gabapentinoids in English general practices and the factors associated with gabapentinoid prescribing, including socioeconomic status and geographical variation at the practice-level to help identify regions and practices that may need more attention. The objectives are:

(1) To quantify the monthly prescribing of gabapentinoids in English general practices from April 2013 to March 2019;
(2) To investigate the trajectory of prescribing gabapentinoids in English general practices from April 2013 to March 2019;
(3) To identify practice-level influential factors that are associated with a higher prescribing rate of gabapentinoids in English general practices in the 2018/19 financial year;
(4) To investigate the geographical variation in prescribing gabapentinoids in English general practices in the 2018/19 financial year.

3.3. Methods

3.3.1. Study design and data sources

This study used aggregated-level data from several publicly available data sources in the UK from April 2013 to March 2019 (Table 3-1). The practice-level prescriptions that were written and dispensed (including medicines' names, dose, and the number of items) in England [137], and practice characteristics such as the number of registrants, the number of females, the number of over 65's, postcodes [138] and Quality and Outcomes Framework (QOF) indicators [139] were retrieved from different portals of NHS Digital [140]. The national population size in England was retrieved from the annual mid-year population estimates from the Office for

National Statistics (ONS) [141]. The IMD decile was extracted from the UK Ministry of Housing, Communities & Local Government measures [135]. The England boundary for mapping was retrieved from the UK Data Service website [142].

The NHS Digital prescribing dataset is a publicly available database that provides detailed information on prescriptions issued in English primary care and were successfully dispensed in any pharmacy in England, Wales, Scotland, Guernsey, Alderney, Jersey, or the Isle of Man [143]. Although actually a 'dispensing' database, it is named a 'prescribing' database by the NHS and many other institutions; hence, it is named ‘prescribing data’ in this study to avoid misunderstanding. The practice-level prescribing data provides the monthly number of items prescribed in general practices for individual products.

The product information in the NHS Digital prescribing database is recorded using British National Formulary (BNF) codes [74]. A BNF code is a unique 15-digit code used to identify drug products. The first nine digits of the BNF code identify a specific chemical substance, and the following six digits further determine the strength, formulation and brand. The first 9-digits of the codes for the study drugs were identified from the BNF code file available on the NHS Digital Practice Level Prescribing webpage. The first 9 digits were then used to identify gabapentinoid prescriptions of all brands, strengths, and preparations (e.g. capsules, tablets, oral solutions) from the NHS Digital prescribing database.

Primary care practices (general practice, community pharmacy, dental and optometry services) [117] that prescribed at least one gabapentinoid preparation from April 2013 to March 2019 were selected as the study subjects. Of these, general practices were used to analyse the quarterly utilisation trajectory from 2013/14 to 2018/19. General practice prescribed gabapentinoid data in the 2018/19

financial year (April 2018 to March 2019) were allocated to the 195 CCGs for the geographical variation analysis where postcodes were used to identify geographical coordinates for each practice (Figure 3-1).

Table 3-1. Sources of data used in this study

Data source	Data category	Time period	Information retrieved from datasets
National Health Services Digital	Practice-level prescribing data [140]	April 2013 to March 2019	Monthly amount of prescribed gabapentin and pregabalin preparations in England
	Practice-level number of registrants [138]	April 2013 to March 2019	Quarterly or monthly number of registrants, and the proportion of female and elderly (age > 65 years) registrants in each practice, postcode of the practice
	Practice-level Quality and Outcomes Framework [139]	April 2018 to March 2019	Annual proportion of obesity, cancer, diabetes, depression, epilepsy, mental health diseases, rheumatoid arthritis and osteoporosis
Ministry of Housing, Communities & Local Government **[142]**	LSOA-level English indices of deprivation	2019	Index of Multiple Deprivation (IMD) deciles
Office for National Statistics **[141]**	National population estimates	2013 to 2018	Annual number of mid-year estimation of England population

Note: LSOA: Lower Layer Super Output Area

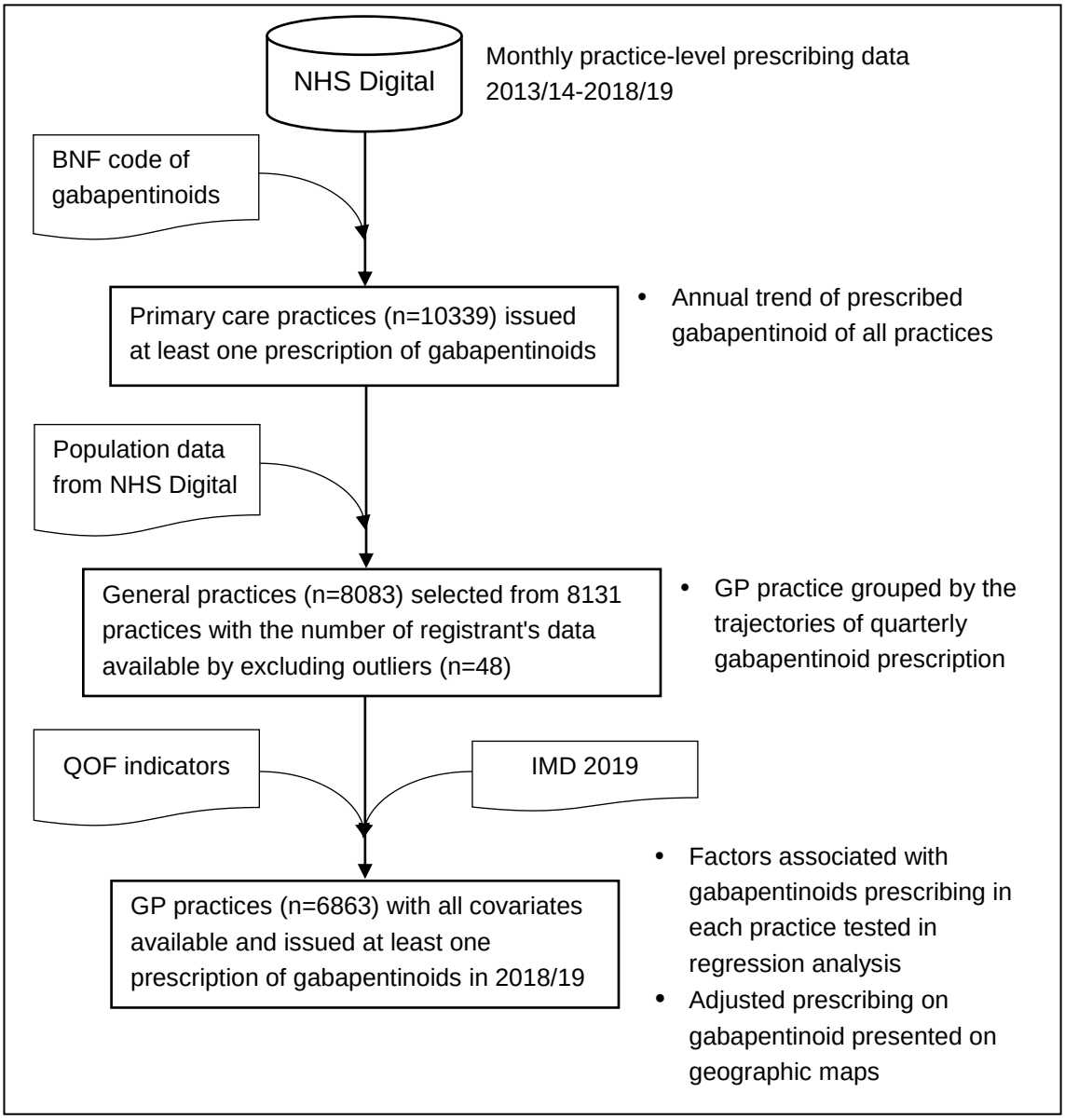


Figure 3-1. Flowchart for the identification of practices prescribing gabapentinoids

Note: NHS: National Health Service; BNF: British National Formulary; IMD: Index of Multiple Deprivation; QOF: Quality and Outcomes Framework; GP: general practitioner

3.3.2. Outcome measures

The monthly utilisation of the study drugs in England was quantified using the Defined Daily Dose (DDD). DDD is a measure of drug utilisation developed by the World Health Organisation (WHO) to compare drug usage between different drugs. It is defined as "*the assumed average maintenance dose per day for a drug used for*

its main indication in adults" [144]. The DDD is used to adjust for the dose variation of drugs in the same category to enable a comparable measurement. For example, gabapentin and pregabalin are both categorised as gabapentinoids but have different recommended daily doses (gabapentin 900 to 3600 mg/day, pregabalin 150 to 600 mg/day), so simply adding up the grams of gabapentin and pregabalin cannot reflect the use of gabapentinoids properly. Alternatively, dividing the actual quantity in grams by the standardised daily dose (DDD) of the drug provides a consistent measure of 'the number of days covered by the quantity (grams) used at the drug's average maintenance dose'. In this example, the DDD for gabapentin is 1.8 grams for oral administration, and the DDD for pregabalin is 0.3 grams for oral administration [145].

The unit dose and quantity of prescribed gabapentinoid records were multiplied and summed separately for gabapentin and pregabalin in each calendar month, and then divided by the DDD published by the WHO [144]. The number of prescribed DDDs of gabapentin and pregabalin was summed to generate the monthly number of DDDs of gabapentinoids (Equation 3-1).

$$\text{Monthly gabapentinoid prescribing rate (DDD/month)} = \sum_{i=1}^{m} \frac{unit\ dose_{\ i} \times quantity_i}{DDD_{gabapentin}} + \sum_{j=1}^{n} \frac{unit\ dose_{\ j} \times quantity_j}{DDD_{pregablin}}$$

Equation 3-1. Monthly gabapentinoid prescribing quantified in Defined Daily Dose

Where i indicates individual gabapentin prescribing record in the month, m is the total number of gabapentin prescribing records in the month, j indicates individual pregabalin prescribing record in the month and n is the total number of pregabalin prescribing records in the month.

The annual gabapentinoid prescribing rate (i.e. DDDs/1000 people/year, as the denominator derived from the national population) in England in each financial year

from 2013/14 to 2018/19 was derived from summing up the annual number of DDDs of prescribed gabapentinoids in all primary care practices and dividing by the corresponding mid-year population estimation of England and then multiplying by 1000 (Equation 3-2).

$$\text{Annual gabapentinoid prescribing rate in England (DDD/1000 people/year)} = \frac{\sum_{i=1}^{12} monthly\ gabapentionid\ prescribing\ in\ England\ in\ DDD_{\ i}}{mid\ year\ population\ estimation\ of\ England} \times 1000$$

Equation 3-2. Annual gabapentinoid prescribing in England adjusted by population

Where i is the individual month of the financial year.

For each general practice, the quarterly prescribing of gabapentinoids (i.e. DDDs/1000 registrants/quarter, as the denominator derived from registrants to practices) was calculated by summing up the monthly number of DDDs of gabapentinoids per quarter from 1 April to 31 March each year, then dividing by the number of patients registered in the practice for the quarter, and further multiplying by 1000 (Equation 3-3).

$$\text{Practice quarterly gabapentinoid prescribing rate (DDD/1000}\ registrants/quarter) = \frac{\sum_{i=1}^{3} monthly\ gabapentionid\ prescribing\ in\ the\ practice\ in\ DDD_{\ i}}{\text{the number of patients registered in the practice for the quarter}} \times 1000$$

Equation 3-3. Quarterly practice gabapentinoid prescribing rate adjusted by practice population

Where i is the individual month of the quarter.

For each general practice, the total DDDs of prescribed gabapentinoids in the financial year 2018/19 was divided by the maximum number of registrants in any

month of the financial year 2018/19 and multiplied by 1000 to calculate the annual number of DDDs/1000 registrants in the year (Equation 3-4).

$$\text{Practice annual gabapentinoid prescribing rate in } 2018/19 \text{ (DDD/1000 } registrants) = \frac{\sum_{i=1}^{12} monthly\ gabapentionid\ prescribing\ in\ the\ practice\ in\ DDD_{\ i}}{\text{maximum monthly number of registrants in the practice in the year}} \times 1000$$

Equation 3-4. Practice gabapentinoid prescribing rate adjusted by practice population in 2018/19

Where i is the individual month of the quarter.

3.3.3. Covariates

Factors associated with gabapentinoid prescribing in each general practice were used as covariates to adjust the annual gabapentinoid prescribing at the practice level in 2018/19. Considering the results of previously published literature [24, 89, 129], these factors included practice-level demographic characteristics (the proportion of females or elderly aged over 65), lifestyle indicators (the proportion of obese registrants or current smokers), disease conditions (the proportion of patients with epilepsy, depression, mental health diseases, diabetes, rheumatoid arthritis, cancer) and socioeconomic status (2019 IMD decile). Each general practice was allocated an IMD decile using its postcode to locate the corresponding LSOA [146]. The IMD score of each LSOA was ranked from most to least deprived, and then divided into ten equal groups, and hence the first IMD decile is the most deprived group [135]. The GP level IMD was used as a proxy to indicate the registrants' IMD under the assumption that people in England usually register at GP practices that are near their living places [147].

3.3.4. Analytical methods

Descriptive analyses were used to summarise the prescription of gabapentinoids with medians and interquartile ranges (IQR). Annual trends of prescribed gabapentinoids in primary care in England from 2013/14 to 2018/19 were presented in a line chart. The group-based Trajectory Model (GBTM) is a finite mixture model approach which was applied to categorise practices into groups, based on their trends in longitudinal quarterly prescribing of gabapentinoids [148, 149]. The estimated mean quarterly prescribing trend of each practice group from the GBTM was presented graphically, and the group membership was mapped geographically. For the GBTM, a censored normal distribution model was applied to the prescription data. The lowest Bayesian Information Criterion (BIC) value [150] was set to identify the polynomial trajectory for each group and the number of practice groups to include in the final model. A minimum group size of 5% of the total number of practices was set to ensure a balanced and comparable sample size in groups [149].

In the financial year of 2018/19, the annual prescribing of gabapentinoids across general practices in England was smoothly mapped using a Spline regression [151]. Multilevel mixed-effects regression was used to identify covariates associated with the prescribing of gabapentinoids in 2018/19 across practices after adjusting for cluster effects of CCGs [152]. The CCG cluster effect is the tendency of practices within the same CCG to behave similarly to each other, due to the common rules and guidance given by the CCG. A fixed effect on the slope of covariates while allowing each CCG to have its own intercepts was applied in the regression analysis. For model selection, the likelihood ratio test was used to compare two nested models while combining with the stepwise forward covariate selection and backward covariate elimination [153, 154].

The results of the multilevel mixed-effect regression analysis were presented as coefficients (CE) and 95% confidence intervals (95% CI). The adjusted CCG-level gabapentinoid prescribing rates from the mixed-effect model were then ranked and further grouped into quintiles and mapped geographically. All data analyses were conducted by STATA v14 (Stata-Corp, Texas, USA, 2015) and the mapping of data was conducted using R (version 3.6.0).

3.4. Results

3.4.1. Trend of annual gabapentinoid prescribing

The number of primary care practices which prescribed at least one gabapentinoid preparation in England was 8,950 in 2013/14 and 8,485 in 2018/19. For these practices, the annual prescription rate of gabapentinoids increased by 70% (2,800 to 4,773 DDD /1000 registrants/year) in England from 2013/14 to 2018/19. Breaking down the overall trend, the annual prescribing rate of gabapentin (1,335 to 2,118 DDD/1000 registrants/year) and pregabalin (1,465 to 2,655 DDD/1000 registrants/year) both increased steadily (Figure 3-2).

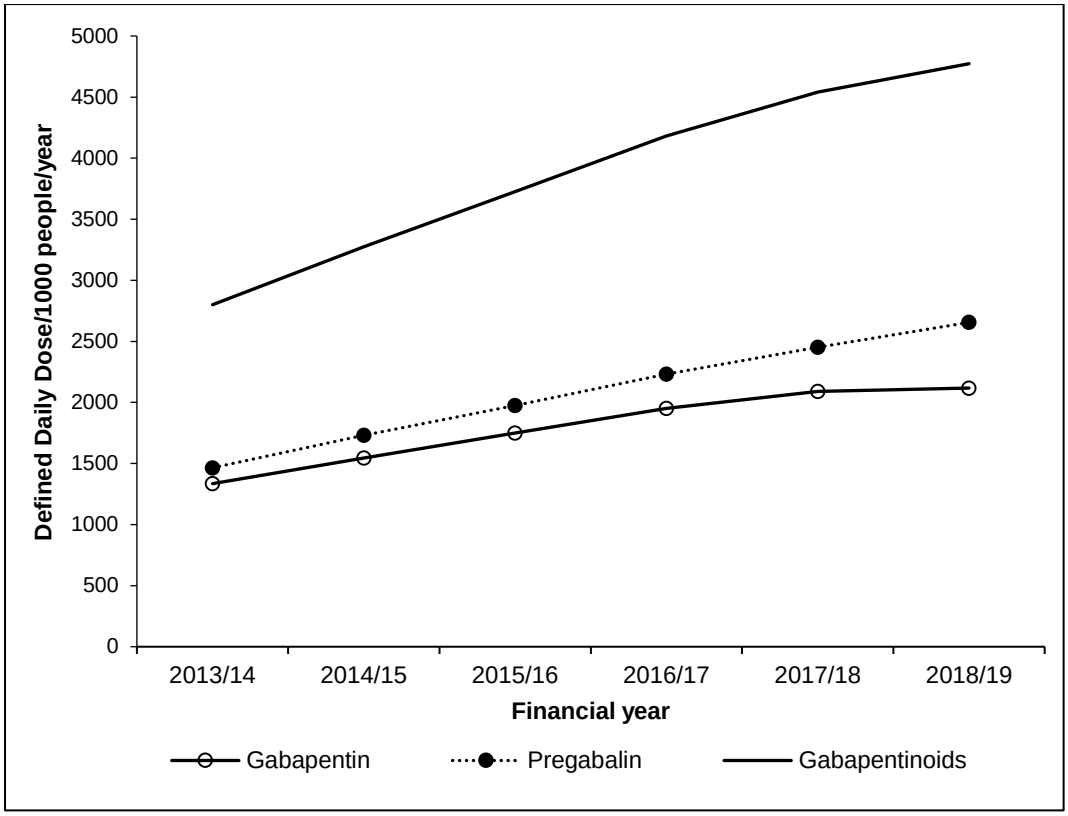


Figure 3-2. Annual gabapentinoid prescribing in primary care practices in England from 2013/14 to 2018/19

3.4.2. Practice trajectory of gabapentinoid prescribing by financial quarter

From April 2013 to March 2019, 8,083 of the 8,131 general practices that had at least one prescription of gabapentinoids were included in the GBTM after excluding 48 practices with a quarterly prescribing rate over 6,000 DDD/1000 registrants/quarter defined as outliers (Figure 3-1). The GBTM allocated the 8,083 general practices into 6 groups with different trajectories of prescription which demonstrated various levels of increments of quarterly gabapentinoids prescribing.

The 792 (9.8%) practices with the highest level of prescribing (Group 1, Figure 3-3) were attributed to the trajectory with the largest quarterly increase of 89.0% from 1,252.9 (95% CI: 1,220.3, 1,285.5) to 2,367.8 (95% CI: 2,335.6, 2,400.0) DDDs/1000 registrants/quarter of prescribed gabapentinoids over the 24 quarters.

Geographically, these practices are mainly situated in the north of England (Figure 3-4). In contrast, the 1,220 (15.1%) practices with the smallest quarterly increase of 74.9% from 233.3 (95% CI: 227.0, 239.6) to 408.2 (95%: 402.3, 414.2) DDDs/1000 registrants/quarter (Group 6, Figure 3-3) are mainly situated in and around London and Birmingham (Figure 3-4).

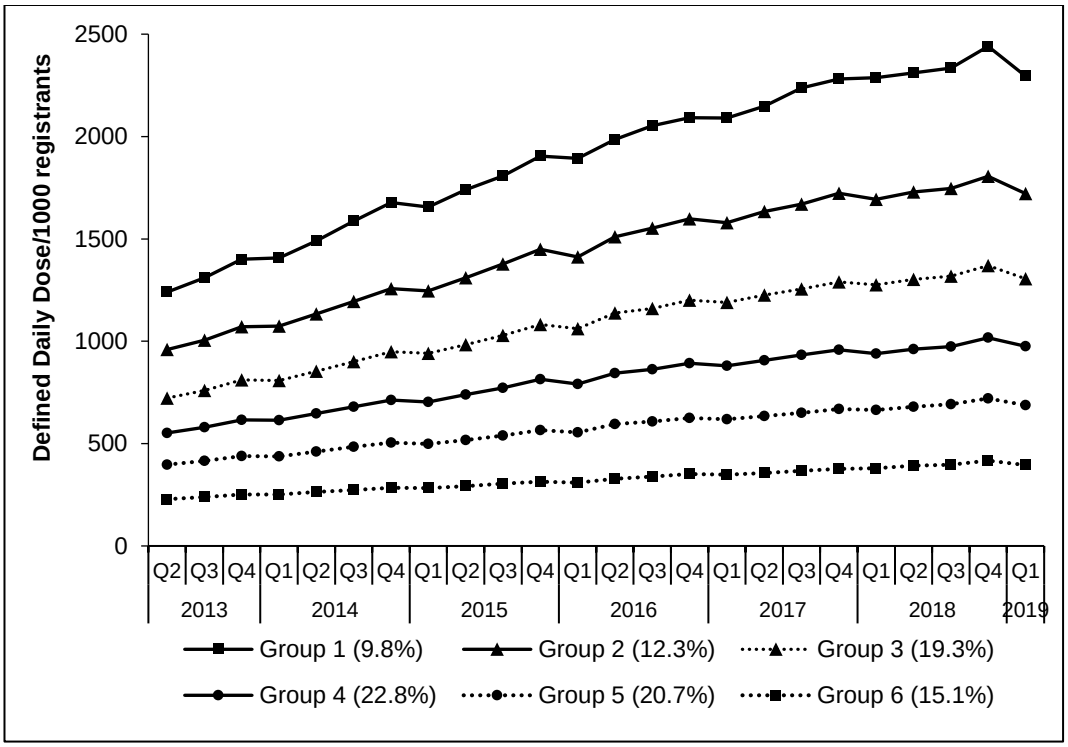
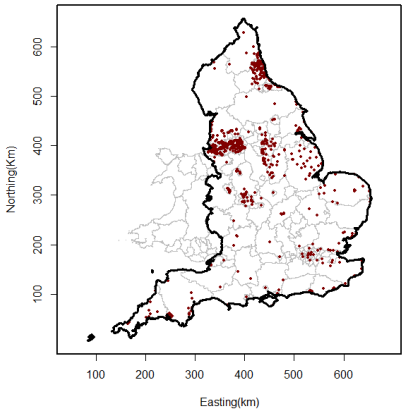
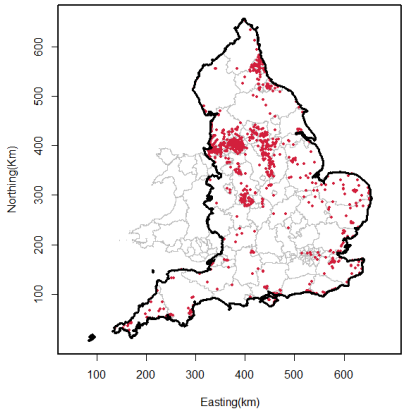


Figure 3-3. Trajectory of the quarterly prescribing of gabapentinoids in 8083 general practices

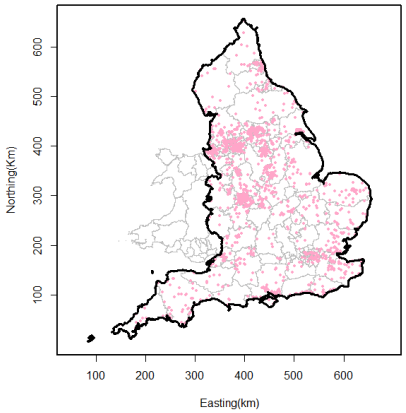
Note: the percentages in the bracket for each group refer to the group size as a percentage of practices among all practices in England



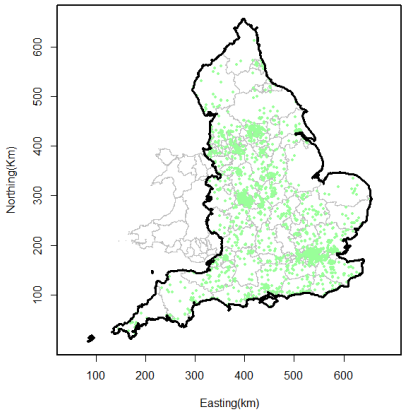
Group 1 (n=792; 9.8%) prescriptions increased by 89.0%



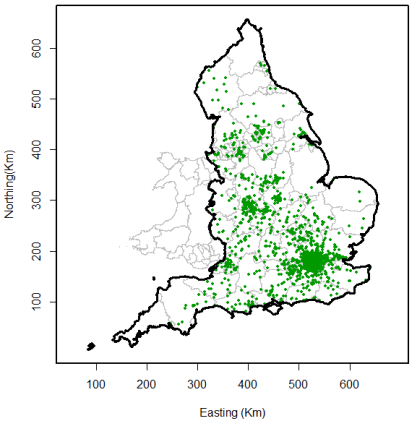
Group 2 (n=994, 12.3%) prescriptions increased by 82.0%



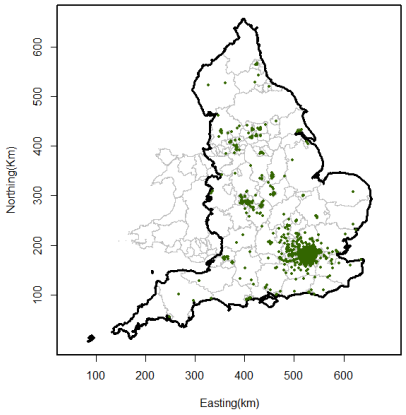
Group 3 (n=1560; 19.3%) prescriptions increased by 82.9%



Group 4 (n=1842; 22.8%) prescriptions increased by 78.5%



Group 5 (n=1672; 20.7%) prescriptions increased by 75.6%



Group 6 (n=1220; 15.1%) prescriptions increased by 75.0%

Figure 3-4. Geographical distribution of general practices categorised in the six trajectory groups from 2013/14 to 2018/19

Note: The groups were categorised by the group-based trajectory model of quarterly practice-level gabapentinoid prescription from 2013/14 to 2018/19 (Figure 3-3). Group 1 had the highest increase, and Group 6 had the lowest increase. The proportion of increase was the difference in gabapentinoids prescription between the 24th quarter and 1st quarter divided by the prescription in the 1st quarter.

3.4.3. Factors related to the prescribing of gabapentinoids

In the 2018/19 financial year, 6,863 general practices that prescribed gabapentinoids had available covariates and contributed to the database continuously for 12 months (Figure 3-1). The multilevel mixed-effect regression suggested that 33% of the prescribing variation was attributed to the CCG cluster effect.

For every decrease in IMD decile (becoming less affluent), the number of prescribed gabapentinoids significantly increased by 202.8 (95% CI: 183.4, 222.2) DDDs/1000 registrants after adjusting for practice characteristics. General practices with high proportions of elderly, obesity, smoking, cancer, depression, epilepsy, mental health disease and rheumatoid arthritis were also significantly associated with increased annual prescribing of gabapentinoids. Among covariates, epilepsy (CE: 1235.8; 95% CI: 1013.9, 1457.7) and rheumatoid arthritis (CE: 476.9; 95% CI: 261.7, 692.0) had greater effects. In contrast, the higher proportions of females (CE: -20.1; 95% CI: -38.7, -1.6) and registrants with diabetes (CE: -48.4; 95% CI: -74.7, -22.2) were significantly associated with fewer gabapentinoid prescriptions (Table 3-2).

Table 3-2. Population characteristics significantly associated with prescribing gabapentinoids in 2018/19 amongst the 6,863 general practices

	Coefficient (95% confidence interval)
Socioeconomic status	
IMD decile	-202.8 (-222.2, -183.4)
Percentage of registrant demographics	
Female	-20.1 (-38.7, -1.6)
Age over 65 years	59.8 (50.0, 69.6)
Percentage of Quality of Outcomes Framework indicators	
Obesity	27.0 (12.2, 41.8)
Smoking	46.4 (35.4, 57.5)
Cancer	87.9 (27.5, 148.2)
Diabetes	-48.4 (-74.7, -22.2)
Depression	34.3 (21.4, 47.2)
Epilepsy	1235.8 (1013.9, 1457.7)
Mental health diseases	101.3 (13.7, 188.9)
Rheumatoid arthritis	476.9 (261.7, 692.0)
Random effects at the CCG level	**Variance (standard deviation)**
CCG intercept	1346533 (1160)
Residual	2817778 (1679)

Note: a. The results were derived from the mixed-effects multiple regression on the annual prescribing of gabapentinoids (DDD/1000 registrants) in 2018/19. Of the 6,863 practices, the median number of registrants was 7,640 (IQR: 4,824, 11,200). The median percentage of female registrants and registrants aged over 65 years was 50.4% (IQR: 49.3%, 51.2%) and 17.7% (IQR: 12.6%, 22.1%), respectively. The median IMD decile in the GP practices was 4 (IQR: 2, 7). The median prescribing rate of gabapentinoids was 4,032 (IQR: 2,739, 5,739) DDD/1000 registrants/year.
b. IMD: Index of Multiple Deprivation, CCG: Clinical Commissioning Group

3.4.4. Geographical variation of prescribed gabapentinoids

In line with the geographical distribution of practices of various trajectory groups (Figure 3-4), the geographic map of gabapentinoid prescriptions in 2018/19 showed that northern England, especially areas around Newcastle and the northwest corridor including Blackpool, Liverpool and Greater Manchester, prescribed greater amounts of gabapentinoids than southern regions (Figure 3-5). The 25% of practices that prescribed the most gabapentinoids were found in large cities, including Newcastle, Manchester, Sheffield, Nottingham and North Birmingham. There were also some practices found on the east and south coastline of England,

such as Brighton and Bournemouth, that were among the top-ranking gabapentinoid prescribers. The 25% of general practices with the lowest prescription rates were found in London and its surrounding areas, and also South Birmingham (Figure 3-5).

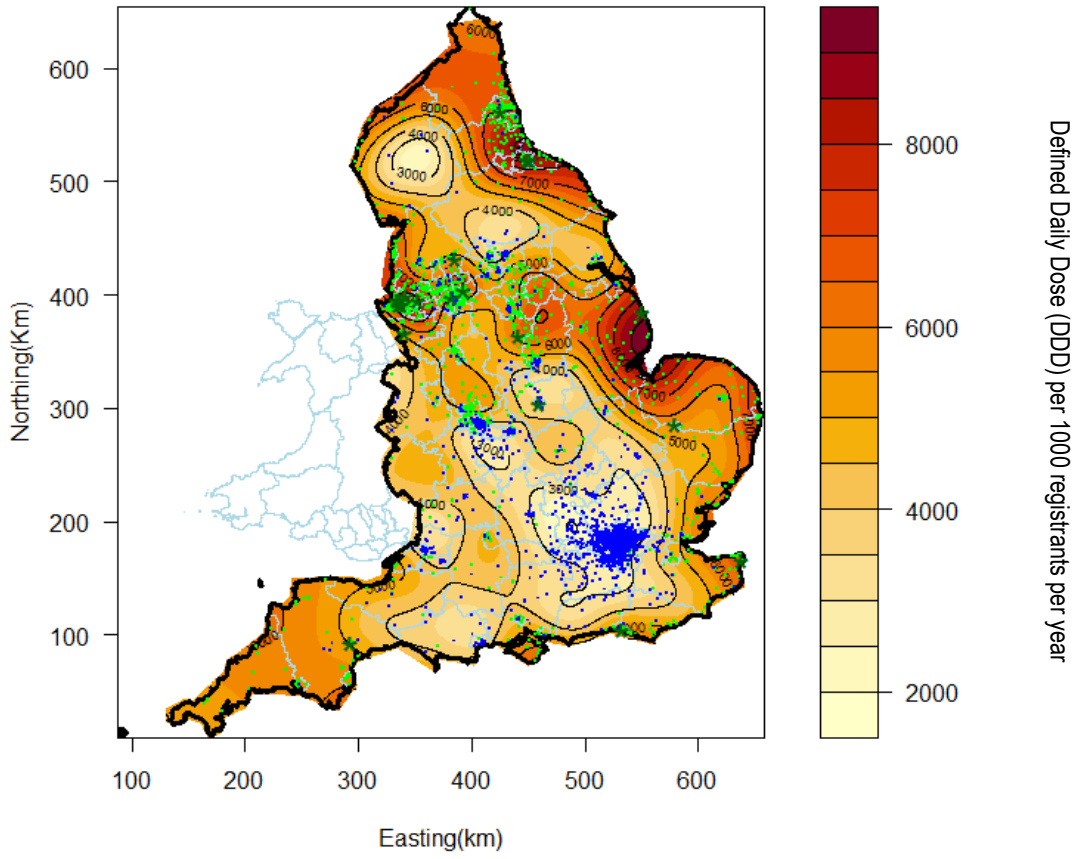


Figure 3-5. Geographical distribution of gabapentinoid prescription rate in 6863 general practices in England in 2018/19

Note: The prescription rate is quantified in general practices, and smoothed by a Spine regression on a geographic map. The England boundary for mapping was retrieved from the UK Data Service website [142]. The blue dots indicate GP practices in the bottom 25% of the prescription rate ranking. The green dots indicate GP practices in the top 25% of the prescription rate ranking. The dark green stars mark the locations of the top 20 GP practices with the highest prescribing rates.

The adjusted gabapentinoid prescription rate of 195 CCGs was estimated using a multilevel model. This CCG-level utilisation, according to the ranking, also showed a geographical variation in England in 2018/19. Practices in the top CCG ranking group which prescribed the most gabapentinoids were concentrated in Newcastle, Manchester, and the surrounding areas (Figure 3-6).

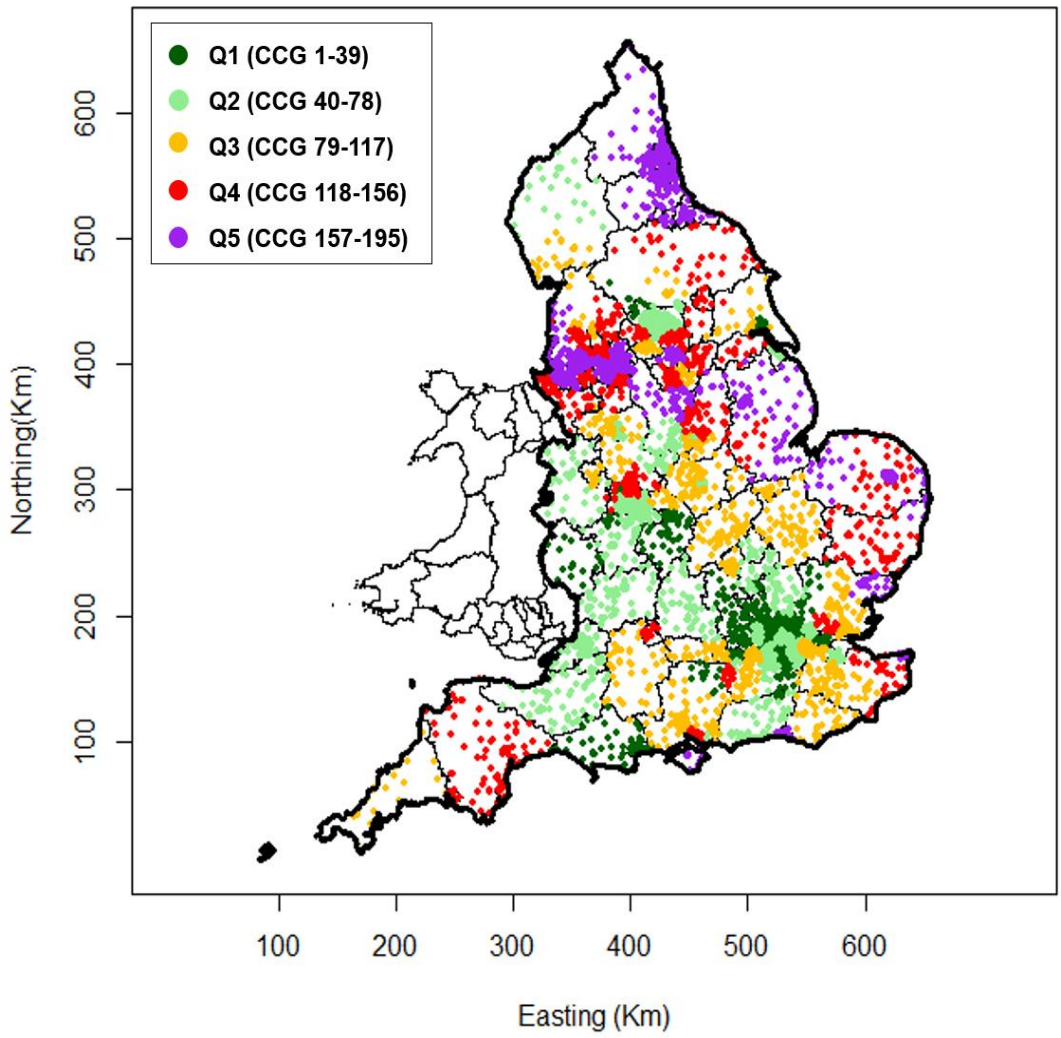


Figure 3-6. Geographical distribution of CCG-level prescription rate in 2018/19 demonstrating by practice location from random CCG effect

Note: The prescription rate is quantified as the Defined Daily Dose (DDD) per 1000 registrants in general practice, adjusted for covariates and the random cluster effect of Clinical Commissioning Groups (CCGs). The adjusted random effects on the gabapentinoid prescription rate of the 195 CCGs attributed from the 6863 GP practices were ranked into quintile groups: Q1 refers to 1-39 CCGs in the quintile with the lowest utilisation, and the utilisation increases in Q2 (40-78 CCGs), Q3 (79-117 CCGs), Q4 (118-156 CCGs), and to top utilisation group of Q5 (157-195 CCGs).

3.5. Discussion

The prescription of gabapentinoids in primary care in England steadily increased from April 2013 until April 2019 when gabapentinoids were classified as controlled drugs. Although there is variation across practices, the gabapentinoid prescribing rate increased in all trajectory groups, and the group with the highest level and the greatest increase in prescribing is found primarily in northern England. Multiple population characteristics, including demographics, the prevalence of disease and socioeconomic status are significantly associated with gabapentinoid prescribing in general practices. The CCG cluster effect also contributes to the variation in gabapentinoid prescribing rates in general practices. After taking all these factors into account, the gabapentinoid prescribing rate still shows a geographical variation, and CCGs located in the north and along the east coastline of England have higher prescribing rates.

Two previously published papers had also found an increasing trend in gabapentinoid prescribing [6, 9]. However, the drug utilisation study by Montastruc *et al.* (2018) used data from a primary care database which covered only approximately 7% of the UK population and is not free from sampling bias [6]. In addition, the ecological study by Green *et al.* (2019) quantified utilisation as the "number of prescriptions per capita" which did not account for dosage and this may bias the results [9]. In contrast, this study adopts an objective measure, the defined daily dose (DDD), to measure the prescribing rate and used national data.

After adjusting for all other available factors, there is still a significant association between socioeconomic status and gabapentinoids prescription rate. The geographical variation in gabapentinoid prescription can be partly explained by socioeconomic status which may contribute to inequity in health care [21]. People living in socioeconomically more deprived areas have less access to health care

services and may have more comorbidities [155], while chronic pain is likely to be one of these common comorbidities [156].

Chronic pain is most highly prevalent in the population who are older, are female, who smoke, are obese and are socioeconomically deprived [24], which are similar factors to gabapentinoid users according to the regression analysis. In this study, the positive and relatively high regression CE value for the QOF indicator for rheumatoid arthritis indicates that gabapentinoids are commonly prescribed for chronic pain. The common off-label use of gabapentinoids for chronic pain also indicates an unmet need for appropriate management of pain conditions [44, 45]. The CCG cluster effect in gabapentinoid prescribing rates indicates a potential difference in prescribing policy between CCGs for pain management.

The geographic map of gabapentinoid prescribing rates in this study is similar to other studies that have mapped prescribed opioid utilisation [134] and heroin and morphine deaths in England [157], with the same areas having high rates of each. The resemblance in geographical distribution between gabapentinoids and opioids [134] augments the previous proposition that the indications (i.e. chronic pain conditions) for prescribing gabapentinoids and opioids are similar, and that gabapentinoids are increasingly co-prescribed with opioids in the UK [6, 158, 159]. A higher opioid prescribing rate has been found to be associated with deprived socioeconomic status, older age, smoking, obesity, and depression in England according to Chen *et al*. (2019) and Curtis *et al.* (2019) [132, 134]. These factors also match the covariates associated with prescribing gabapentinoids in this study. Two Canadian studies found that gabapentinoid utilisation is associated with an increased risk of opioid-related death in opioid users [22, 23]. The potential for gabapentinoid addiction has been explored in both laboratory models and clinical studies [160]. Therefore, the increased risk of drug-related death in gabapentinoid

users may be attributable to the co-prescribing of opioids for chronic pain, or substance misuse and abuse issues. Nevertheless, the association between gabapentinoid utilisation patterns (e.g. co-prescription of opioids) and potential gabapentinoid-related harms remain unclear.

This study used data from several publicly available national databases including: a) prescriptions written and dispensed in primary care in England; b) an official measurement of socioeconomic status by area; and c) the practice-level prevalence of diseases. Therefore, the prescribing and population characteristics cover the whole population of England. Gabapentinoid prescriptions in this study were measured using DDD, which provides a comparable measure and can also be used in cross-nation comparisons. The group-based trajectory model provides additional insights into the variation between practices. The multilevel mixed-effect regression model adjusts for multiple factors and considered the significant CCG cluster effect on gabapentinoid prescribing to generate robust results. Both raw and adjusted prescription rates were presented on geographic maps to support the main findings visually.

However, there are several limitations to this study. Firstly, this study used aggregated prescription data and population characteristics at the practice level to explore the hypothesis rather than investigating the association at the individual patient level. Therefore, the results should be interpreted cautiously as no patient-level conclusions can be drawn. Secondly, the dataset only obtained gabapentinoids from prescribing data instead of other access routes (e.g. online purchases or illicit diversion), and hence may underestimate the overall gabapentinoid usage in England. However, this amount should be minimal due to the nature of accessing health care in the NHS. Thirdly, QOF indicators were initially designed for auditing the quality of services and do not cover all indications of

gabapentinoid use (e.g. neuropathic pain and other chronic pain conditions), which may result in unmeasured bias in the regression analysis.

The prescribing of gabapentinoids increased dramatically in England from 2013 and this has caused concerns to be raised about potential harm. Multiple factors have been found to be associated with the prescribing of gabapentinoids in general practices. There is a significantly positive association between socio-economic deprivation and prescribing gabapentinoids after adjusting for the effect of demographic characteristics, diseases, and CCG policies. This association may be linked with opioid utilisation and drug-related deaths. Although gabapentinoids have been classified as controlled drugs in the UK since April 2019, the factors driving the large prescribing rate and determinants of gabapentinoid-related harms still warrant further investigation. To optimise gabapentinoid prescribing for chronic pain management, further research is needed to explore the utilisation patterns of gabapentinoids, and the risk factors for the safety of gabapentinoids by using patient-level data. The regional variation and CCG cluster effect found in gabapentinoid prescribing in England suggest that localised interventions by authorities may work effectively to mitigate medication use problems. The effectiveness of local interventions needs further research.

Chapter 4. The impacts of gabapentinoid classification on the prescribing of gabapentinoids and pain-related medicines in English primary care

4.1. Introduction

The Health and Social Care Board raised initial concerns about gabapentinoid misuse and abuse in 2014 because of the growing misuse and abuse in Northern Ireland, probably due to the euphoric effect of pregabalin [12]. Then, on the 14th of January 2016, the Advisory Council on the Misuse of Drugs (ACMD), a non-departmental public advisory body that makes recommendations to the government on the control of dangerous drugs, issued a letter to the home office to advise of the harm of gabapentinoids and suggested controlling gabapentinoids as Class C substances [12]. Following the ACMD's recommendations, the UK government passed a law to classify gabapentinoids as controlled drugs in April 2019 to reduce the risk of drug misuse, abuse and diversion in the UK [161]. Under the new regulation, gabapentinoids are dispensed for hand-signed prescriptions only, and gabapentinoid prescriptions are only valid for 28 days after the date on the prescription, and no emergency supply of gabapentinoids is permitted [162].

However, the efficacy of the classification policy in reducing gabapentinoid misuse and abuse has not been thoroughly investigated. The gabapentinoid classification policy may have had a different impact on prescribing gabapentinoids for each of the trajectory practice groups identified in Chapter 3 (Section 3.4.2). Understanding the impact of the gabapentinoid classification on gabapentinoid prescribing can inform future regional policies to optimise gabapentinoid prescribing. Therefore, it is hypothesised that the gabapentinoid classification policy has decreased the prescribing of gabapentinoids.

The impact of the Coronavirus Disease 2019 (COVID-19) pandemic and related lockdown on healthcare provision and accessibility since March 2020 altered prescribing and dispensing procedures in primary care [163-167]. This could also influence the prescribing trend of gabapentinoids. Therefore, the impact of the COVID-19 lockdown must be acknowledged when evaluating the impact of the classification policy on prescribing gabapentinoids.

The classification of gabapentinoids may also influence prescribing of other pain medications as they could be considered a substitution for gabapentinoids [44]. Gabapentinoids were recommended as one of the first-line treatments for neuropathic pain by the National Institute for Health and Care Excellence (NICE) and are widely used off-label to manage other chronic pain conditions [6] [44]. Other first-line drug therapies for neuropathic pain include amitriptyline and duloxetine. Additionally, in 2010 the European Federation of Neurological Societies guidelines on the pharmacological treatment of neuropathic pain included tricyclic antidepressants (TCAs), norepinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine) and gabapentinoids as the first-line therapy for painful polyneuropathy, while amitriptyline and gabapentinoids were recommended as the first-line therapy for central neuropathic pain [168]. After the classification of gabapentinoids, prescriptions for other therapies to treat neuropathic pain such as amitriptyline and duloxetine may have increased due to a switch from controlled gabapentinoids to free-to-prescribe antidepressants [44].

Since chronic pain often coexists with symptoms of depression, anxiety and insomnia [169], the prescribing of other pain management medicines such as opioids, benzodiazepines and antidepressants, may also have been influenced by the classification of gabapentinoids. Benzodiazepines are widely used to control

distress, anxiety, fearfulness, and disordered sleep patterns that are likely to co-exist with chronic pain symptoms [67]. A study conducted in a US outpatient interdisciplinary pain rehabilitation program found that 248 (29%) of the 847 consecutive patients admitted to the program during 2013-2014 were taking benzodiazepines [68]. Similarly, the use of antidepressants is also common in managing chronic pain, especially tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) [170, 171]. Therefore, the prescribing of these pain-related medicines might experience a change after the gabapentinoid classification as patients might substitute gabapentinoids with other pain medications.

4.2. Aim and objectives

This ecological study aims to investigate the effect of the gabapentinoid classification policy in April 2019 on the prescribing of gabapentinoids and other pain medications in English general practices. The objectives are:

(1) To evaluate the monthly prescribing trends of gabapentinoids, opioids, antidepressants, and benzodiazepines in English general practices from April 2013 to May 2021;
(2) To investigate the impact of the gabapentinoid classification on the prescribing of gabapentinoids and other pain-related medications in English general practices;
(3) To explore the impact of the gabapentinoid classification on the prescribing of gabapentinoids by the trajectory groups of general practices identified in Section 3.4.2, Chapter 3.

4.3. Methods

4.3.1. Study design and data sources

This ecological study took a quasi-experimental approach and conducted segmented regressions [172] on the monthly prescribing of gabapentinoids, opioids, benzodiazepines and antidepressants between April 2013 and May 2021 to evaluate the impact of the gabapentinoid classification policy.

This study used aggregated-level prescribing data in English general practices from the NHS Business Service Authority (BSA) and population statics from NHS Digital [143]. The NHS BSA English Prescribing Dataset (EPD) was used to extract the monthly prescriptions of gabapentinoids, opioids, benzodiazepines, and antidepressants that were dispensed from April 2013 to May 2021 in England. The monthly number of patients registered at GP practices in England between April 2013 and May 2021 was obtained from NHS Digital [138]. Both the NHS BSA EPD and the NHS Digital population data are publicly available, and the use of aggregate-level data is exempt from ethical approval.

Prescription data in the NHS BSA EPD was managed by NHS Digital before April 2020, but was transferred to the NHS BSA in April 2020 and since then was continued to be released monthly by the NHS BSA [143]. Therefore, the data and data structure of the NHS BSA EPD is the same as the NHS Digital prescribing database as mentioned in Chapter 3 (Section 3.3.1).

4.3.2. Study subjects

General practices in England that prescribed at least one of the four categories of study medications (i.e., gabapentinoids, opioids, benzodiazepines, and

antidepressants) between April 2013 and May 2021 were included in this study. The monthly prescriptions issued by these general practices were quantified for the four drug groups to form four time-series groups for further study. General practices that prescribed any gabapentinoids between 2013 and 2019 were divided into six groups by their gabapentinoid prescribing trajectory from April 2013 to March 2019, identified by a trajectory model in Chapter 3 (Figure 4-1) [148].

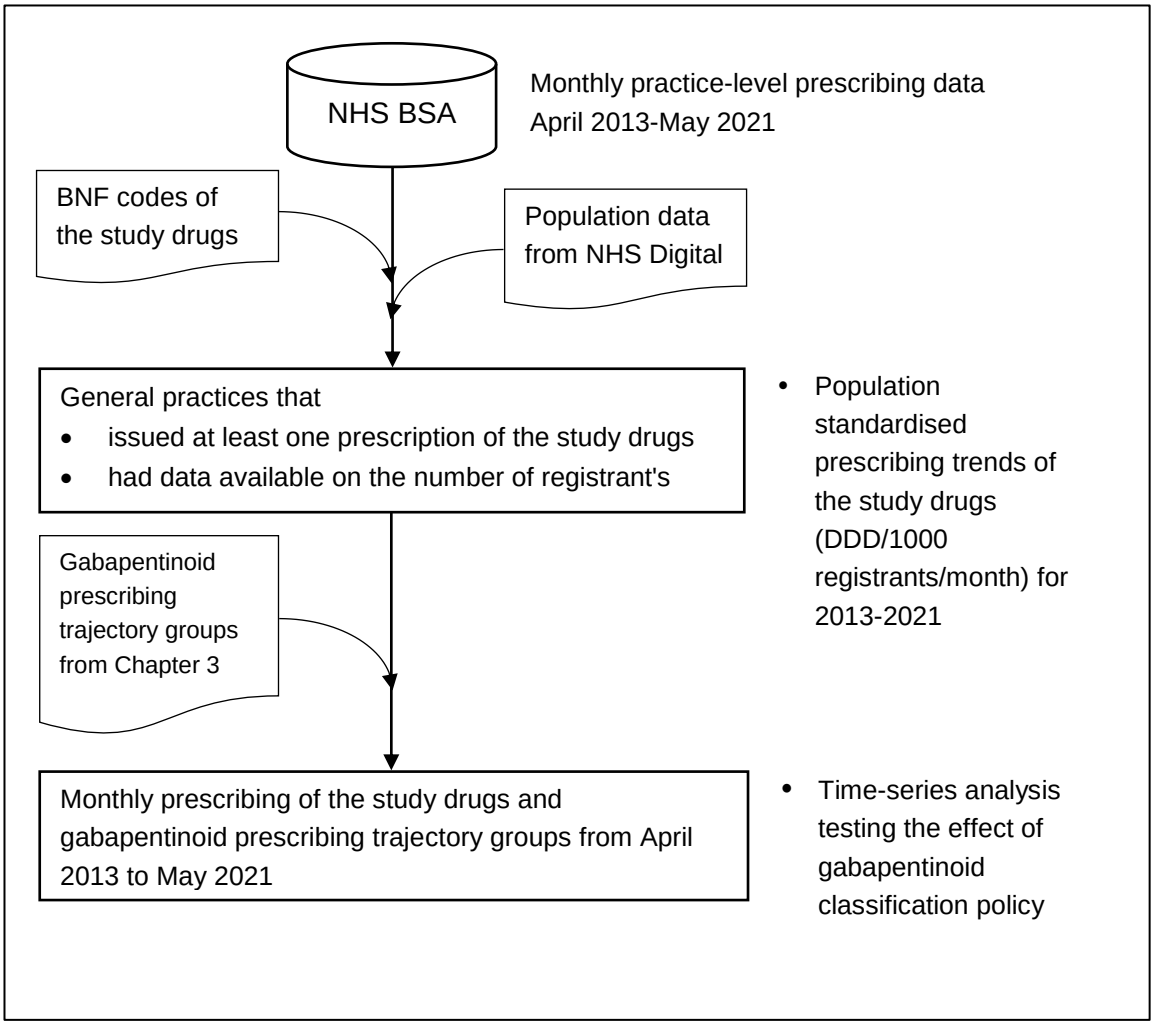


Figure 4-1. Flowchart for identifying practices prescribing studied drugs

Note: NHS: National Health Service; BNF: British National Formulary; DDD: Defined Daily Dose; GP: general practitioner

4.3.3. Outcome measures

The monthly prescribing records for individual products in English general practices between April 2013 and May 2021 were extracted from the EPD. For each record extracted, the quantity was multiplied by the unit dose (i.e., grams or milligrams), and divided by the corresponding DDD published by the World Health Organisation [144]. To generate a standardised monthly prescribing rate for each product (in DDD/1000 registrants/month), all records for that product in the month were summed together and then divided by the number of patients registered to GP practices in England in that month and multiplied by 1000 (Equation 4-1) [144]. Then the standardised monthly prescribing rates of different products were summed by drug category or subcategory to generate category prescribing rates.

$$\text{Standardised prescribing rate of a product (DDD/1000 registrants/month)} = \frac{\sum_{i=1}^{m} \frac{unit\ dose_{\ i} \times quantity_i}{DDD_{product}} \times 1000}{Number\ of\ patients\ registered\ to\ GPs\ in\ England\ in\ the\ month}$$

Equation 4-1. Monthly prescribing rate of a product in English primary care adjusted by registrants

Where i indicates an individual prescribing record of the product in the month, m is the total number of prescribing records of the product in England for the month.

The standardised monthly prescribing rate of gabapentinoids was also calculated for the six trajectory groups for further analysis. The categories of opioids, benzodiazepines, and antidepressants were further divided into subcategories based on indications or pharmacological mechanisms (Appendix 1). Opioids were divided into three groups: strong opioids, weak opioids, and drugs for opioid dependence. Tramadol, a strong opioid with dual opioid and monoaminergic mechanisms, was quantified alone as tramadol has fewer side effects than other opioids, and is likely to be a substitution for gabapentinoids in chronic pain management [173]. Benzodiazepines were grouped using their primary indications

in the BNF dictionary into hypnotics, anxiolytics and anti-epileptic drugs [8]. Antidepressants were grouped by their pharmacology mechanisms into tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and other antidepressant drugs. Amitriptyline, a TCA, was quantified separately because it is the first-line therapy for neuropathic pain recommended by NICE, meaning it is particularly likely to substitute gabapentinoid use [44].

4.3.4. Analytical methods

The standardised monthly prescribing rate (DDD/1000 registrants/month) for gabapentinoids, opioids, benzodiazepines, antidepressants and their subgroups (Appendix 1) from April 2013 to May 2021 were presented as line charts and descriptive statistics. Segmented regression (i.e. interrupted time-series analysis, ITSA) was applied to assess the impact of the gabapentinoid classification policy on the monthly time-series prescription data for four drug categories and eleven subcategories. The classification of gabapentinoids in April 2019 was an immediate one-point intervention that fulfils the requirement for ITSA that the intervention had a relatively quick effect on the outcomes [174]. Each time series contained 72 data points before and 26 data points after the intervention, which is sufficient for ITSA analyses [172]. ITSA was applied to the prescribing series of gabapentinoids, opioids, benzodiazepines and antidepressants (Model 1) and also to the six trajectory groups of prescribing gabapentinoids as generated in Chapter 3 (Model 2) from April 2013 to May 2021.

ITSA is a quasi-experimental design [175] that observes the impact of an intervention on the trend of a continuous sequence of observations in the study population [174] using the assumptions that: the pre-intervention trend is linear, the

ITSA model is at most slowly influenced by unmeasured time-varying confounders, and the residuals have no autocorrelation [175, 176]. Twelve data points before and after the intervention are recommended as a sufficient sample size, although not rigorously proven in power estimation [172]. A balanced distribution of data points before and after the intervention can increase the statistical power of ITSA [177].

The standard segmented regression model of ITSA is as follows [174]:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \varepsilon_t$$

Where Y_t is the outcome at time t, T is the time elapsed from the start of the study, and X_t is a dummy variable indicating either the pre-intervention period or the post-intervention period (i.e. 0 or 1). The β coefficients in the equation indicate the trend or change of the observation over time. β_0 shows the baseline level at T=0, β_1 represents the trend over the observation time and can be interpreted as the underlying pre-intervention trend, β_2 is the level change at the intervention, and β_3 is the trend change after the intervention [174]. ε_t is the residual of the regression.

The β coefficients in the ITSA are reported with 95% confidence intervals (95% CI). The slope of the prescribing trend after the intervention is calculated by adding the trend before the intervention (β_1) to the trend change after the intervention (β_3).

Autocorrelation of residuals in the ITSA segmented regression model would mean the observations in the dataset are not independent, which would invalidate the model fitting. The Durbin-Watson test (DW test) was used to test for autocorrelation in the residuals [172]. An ordinary least squares (OLS) linear regression producing Newey–West standard errors was applied as the initial model [176]. If the residuals of the OLS linear regression result showed autocorrelation in residuals, a generalised least-squares method (Prais-Winsten autoregressive model with one lag) was applied instead to remove the correlation between first-order errors [176].

Three sensitivity analyses were conducted to test the robustness of the results regarding gabapentinoid prescribing only (Model 1). Two sensitivity analyses were conducted by including additional interventions that might influence gabapentinoid prescribing in the model: the first COVID-19 lockdown on 23 March 2020 with the intervention point set as 1 April 2020 in the ITSA (Sensitivity analysis 1), and the public letter from the Advisory Council on the Misuse of Drugs raising concerns about gabapentinoid prescribing in January 2016, with the intervention point set as February 2016 (Sensitivity analysis 2). A third sensitivity analysis applied a shorter time series from February 2017 to May 2021 to balance the data points before and after the intervention so as to test the stability of results (Sensitivity analysis 3).

4.4. Results

4.4.1. Impact of gabapentinoid classification on gabapentinoid prescribing

The monthly gabapentinoid prescribing trend plateaued after April 2019, despite a noticeable steady increase before the classification (Figure 4-2). This pattern was also observed in the six trajectory groups of general practices' gabapentinoid prescribing trends (Figure 4-3). The pregabalin prescribing rate (107.6 to 223.3 DDD/1000 registrants/month) was higher than gabapentin (98.9 to 153.2 DDD/1000 registrants/month) over the 8-year from April 2013 to May 2021 (Figure 4-2).

The monthly gabapentinoid prescribing trend continued to increase after April 2019, though the noticeable rate of increase reduced after classification (Figure 4-2). The classification of gabapentinoids in April 2019 significantly reduced the level of prescribed gabapentinoids at the intervention (β_2: -25.23; 95% CI: -38.78, -11.69; P<0.001) (Table 4-1, Figure 4-3). The trend of prescribed gabapentinoids

significantly reduced after April 2019 (β_3: -1.89; 95% CI: -2.67, -1.12; P<0.001), which is a clear contrast to the rapidly increasing trend before the classification (β_1: 2.56; 95% CI: 2.40, 2.73; P<0.001) (Table 4-1, Figure 4-3). However, despite the decrease in slope after the classification, the trend (calculated trend: $\beta_1 + \beta_3 = 0.67$) of monthly prescribed gabapentinoids continued to increase after the classification in April 2019.

The classification significantly reduced the level of monthly prescribed gabapentin (β_2: -17.54; 95% CI: -24.57, -10.51; P<0.001) and pregabalin (β_2: -8.80; 95% CI: -13.80, -3.80; P<0.001) at the point of the classification of gabapentinoids. The policy had a more substantial impact on the trend of gabapentin prescribing (β_3: -1.12; 95% CI: -1.53, -0.72; P<0.001) than pregabalin (β_3: -0.74; 95% CI: -1.04, -0.45; P<0.001). After the classification, only the trend (calculated trend: $\beta_1 + \beta_3 = 0.79$) of monthly prescribed pregabalin remained increasing.

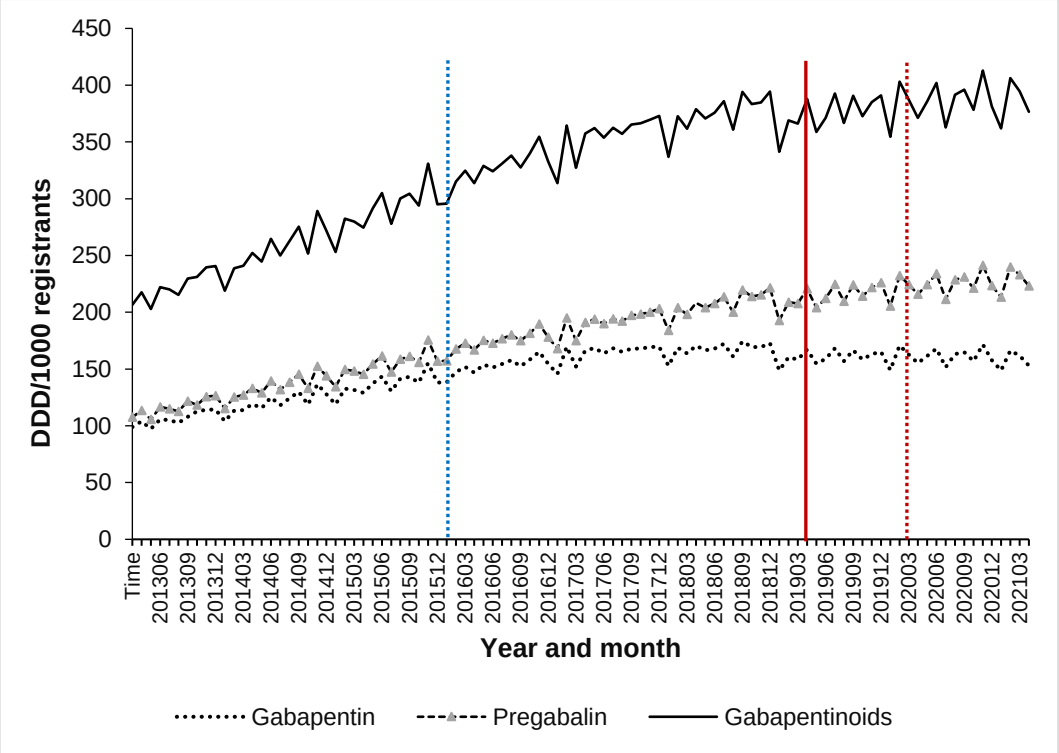


Figure 4-2. Monthly gabapentinoid prescribing in general practices in England from April 2013 to May 2021

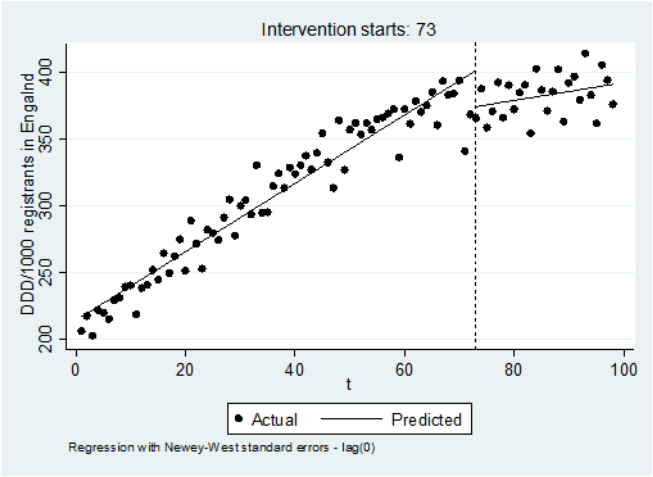
Note: the solid red vertical line marks the classification of gabapentinoids in April 2019, the dotted blue vertical line marks the ACMD public letter in January 2016, and the red vertical line marks the first COVID-19 lockdown in March 2020.

Table 4-1. The impact of gabapentinoid classification in April 2019 on gabapentinoid prescribing from April 2013 to May 2021

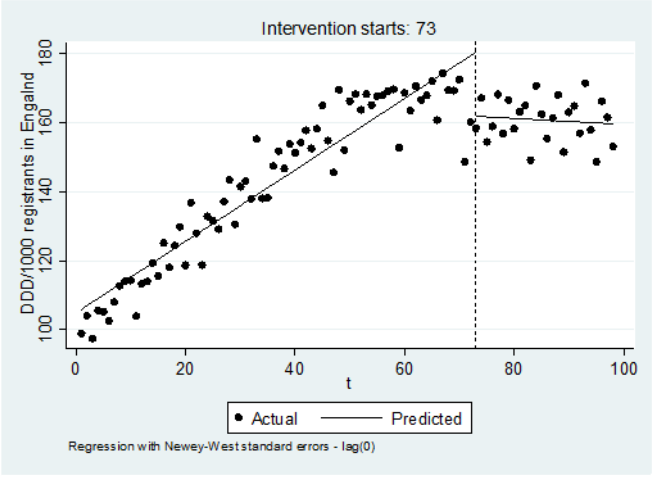
	Trend in pre-policy period (β_1)	Policy impact on the level at the point of intervention (β_2)	Trend change in post-policy period (β_3)
Model 1			
Gabapentinoids	2.56 (2.40, 2.73)*	-25.23 (-38.78, -11.69)*	-1.89 (-2.67, -1.12)*
Gabapentin	1.04 (0.95, 1.12)*	-17.54 (-24.57, -10.51)*	-1.12 (-1.53, -0.72)*
Pregabalin	1.53 (1.47, 1.59)*	-8.80 (-13.80, -3.80)*	-0.74 (-1.04, -0.45)*
Model 2			
Gabapentinoids			
Group 1	0.85 (0.80, 0.89)*	-9.36 (-12.77, -5.95)*	-0.39 (-0.59, -0.19)*
Group 2	1.56 (1.46, 1.65)*	-14.36 (-22.21, -6.50)*	-0.96 (-1.41, -0.51)*
Group 3	2.23 (2.09, 2.37)*	-20.62 (-32.13, -9.11)*	-1.41 (-2.07, -0.75)*
Group 4	3.06 (2.87, 3.26)*	-28.05 (-43.93, -12.16)*	-2.25 (-3.16, -1.34)*
Group 5	4.09 (3.82, 4.36)*	-37.62 (-59.80, -15.44)*	-3.34 (-4.61, -2.06)*
Group 6	5.66 (5.31, 6.01)*	-51.72 (-80.77, -22.67)*	-5.57 (-7.24, -3.90)*
Gabapentin			
Group 1	0.27 (0.25, 0.30)*	-6.05 (-8.16, -3.94)*	-0.23 (-0.36, -0.11)*
Group 2	0.60 (0.55, 0.65)*	-9.34 (-13.24, -5.45)*	-0.60 (-0.82, -0.37)*
Group 3	0.90 (0.83, 0.97)*	-14.59 (-20.52, -8.65)*	-0.86 (-1.20, -0.52)*
Group 4	1.28 (1.18, 1.38)*	-20.49 (-28.96, -12.02)*	-1.37 (-1.85, -0.88)*
Group 5	1.77 (1.63, 1.92)*	-27.76 (-39.57, -15.95)*	-1.94 (-2.62, -1.26)*
Group 6	2.21 (2.03, 2.39)*	-37.18 (-52.08, -22.28)*	-2.89 (-3.74, -2.03)*
Pregabalin			
Group 1	0.57 (0.55, 0.59)*	-2.90 (-4.58, -1.22)*	-0.16 (-0.26, -0.06)*
Group 2	0.96 (0.92, 1.00)*	-5.54 (-8.49, -2.58)*	-0.35 (-0.53, -0.17)*
Group 3	1.33 (1.28, 1.38)*	-6.79 (-11.05, -2.53)*	-0.53 (-0.79, -0.28)*
Group 4	1.78 (1.71, 1.85)*	-8.79 (-14.39, -3.19)*	-0.85 (-1.19, -0.52)*
Group 5	2.32 (2.22, 2.42)*	-11.69 (-19.83, -3.54)*	-1.36 (-1.84, -0.87)*
Group 6	3.45 (3.32, 3.59)*	-18.12 (-28.97, -7.27)*	-2.62 (-3.26, -1.97)*

*Note: (1) The β_1, β_2 and β_3 are coefficients from the linear regression with the appropriate residual optimisation models. In model 2, group 1 is the group of general practices with the lowest level and the lowest rate of increase of gabapentinoid prescribing between April 2013 and March 2019; group 6 is the group of general practices with the highest level and the highest rate of increase of gabapentinoid prescribing. (2) The coefficients are presented with their 95% confidence interval (95% CI). (3) * represents a P-value lower than 0.05.*

(a) Gabapentinoids



(b) Gabapentin



(c) Pregabalin

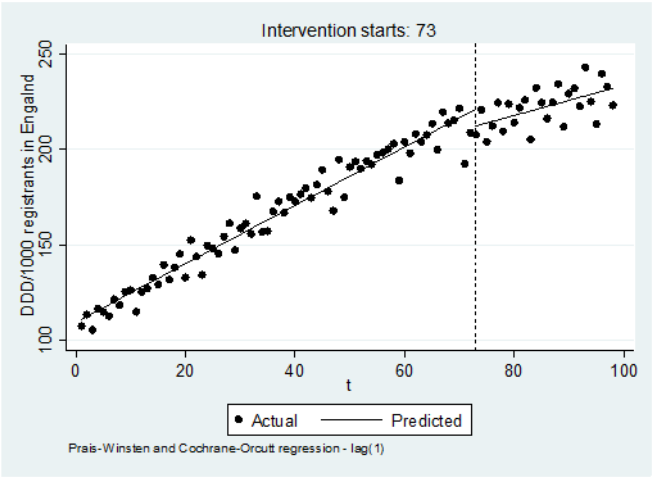


Figure 4-3. Monthly gabapentinoid prescribing before and after gabapentinoid classification in April 2019

Note: (1) the x-axis is the number of months from April 2013 (1) to May 2021 (98); (2) the vertical dotted line marks the time point of the gabapentinoid classification (73)

Similar trends were observed in the six trajectory groups (Figure 4-4). The gabapentinoid classification significantly reduced the level and trend of prescribing gabapentin and pregabalin in all trajectory groups (Table 4-1).

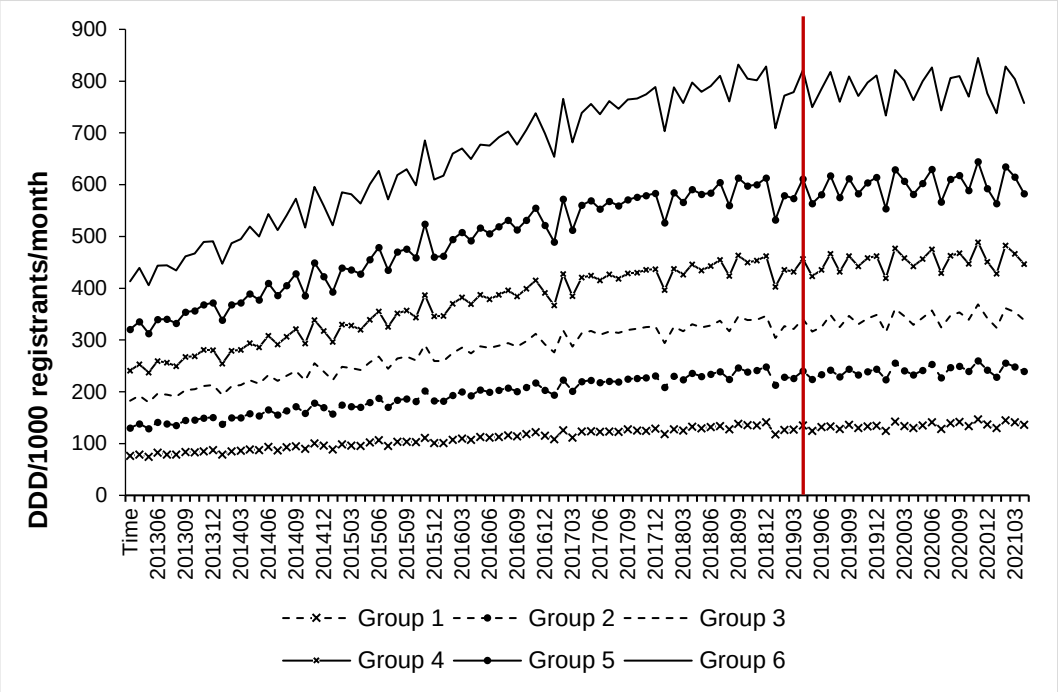


Figure 4-4. Monthly gabapentinoid prescribing stratified by trajectory groups of general practices in England from April 2013 to May 2021

Note: the solid red vertical line is the classification of gabapentinoids on April 2019

The results of sensitivity analysis 1 mitigate the trend change after the gabapentinoid classification in the primary analysis and result in a non-significant trend change in gabapentinoid prescribing (β_3:-1.29; 95% CI: -3.75, 1.17; P=0.300) when including the effect of lockdown due to COVID-19 on 23 March 2020 in the ITSA model. However, the immediate reduction effect of the policy (i.e. level change) was still significant (β_2: -29.07; 95% CI: -48.37, -9.78; P=0.004) (Table 4-2 (a)).

The publication of the ACMD letter had a significant impact on the trend of prescribing gabapentinoid (β_3: -1.25; 95% CI: -1.86, -0.63; P<0.01) and the level of

gabapentin prescribing (β_2: 6.00; 95% CI: 0.01, 12.00, P=0.05). The classification of gabapentinoids had no significant effect on the level of gabapentinoid prescribing (β_4:-13.08, 95% CI: -26.86, 0.69, P=0.060) after the impact of the ACMD letter is included in the model, which implies a preceding effect of the ACMD letter (Table 4-2 (b)). In sensitivity analysis 3, the impact of the policy was found to be non-significant when the study period is reduced to February 2017-May 2021 (Table 4-2 (c)).

Table 4-2. Sensitivity analyses on gabapentinoid prescribing considering other interventions and varying available data points

(a) Impact of the gabapentinoid classification policy and the COVID-19 first lockdown

	Trend in pre-policy period (β_1)	**Policy impact on level (β_2)**	**Trend change in post-policy period (β_3)**	**Lockdown impact on level (β_4)**	**Trend change in post-lockdown period (β_5)**
Gabapentinoids	2.56 (2.40, 2.73)*	-29.07 (-48.37, -9.78)*	-1.29 (-3.75, 1.17)	-1.14 (-24.10, 21.82)	-0.92 (-4.05, 2.21)
Gabapentin	1.04 (0.95, 1.12)*	-19.13 (-29.15, -9.11)*	-0.87 (-2.15, 0.41)	-0.56 (-12.49,11.36)	-0.38 (-2.00,1.25)
Pregabalin	1.53 (1.44, 1.61)*	-9.94 (-19.67, -0.21)*	-0.42 (-1.66, 0.82)	-0.58 (-12.16, 11.00)	-0.54 (-2.12,1.03)

(b) Impact of the ACMD letter and the gabapentinoid classification policy

	Trend in pre-letter period (β_1)	**Letter impact on level (β_2)**	**Trend change in post-letter period (β_3)**	**Policy impact on level (β_4)**	**Trend change in post-policy period (β_5)**
Gabapentinoids	3.09 (2.63, 3.56)*	7.66 (-4.97, 20.29)	-1.25 (-1.86, -0.63)*	-13.08 (-26.86, 0.69)	-1.18 (-1.98, -0.37)*
Gabapentin	1.39 (1.16, 1.61)*	6.00 (0.01, 12.00)*	-0.86 (-1.15, -0.57)*	-8.97 (-15.51, -2.44)*	-0.61 (-1.00, -0.23)*
Pregabalin	1.71 (1.46, 1.96)*	1.66 (-5.11, 8.43)	-0.39 (-0.72, -0.06)*	-4.11 (-11.50, 3.27)	-0.56 (-0.99, -0.13)*

(c) Impact of the gabapentinoid classification policy on the data points between February 2017 and May 2021

	Trend in pre-policy period (β_1)	**Policy impact on level (β_2)**	**Trend change in the post-policy period (β_3)**
Gabapentinoids	1.37 (0.79, 1.94)*	-9.35 (-21.64, 2.95)	-0.65 (-1.45, 0.15)
Gabapentin	0.15 (-0.13, 0.42)	-5.61 (-11.48, 0.25)	-0.21 (-0.60, 0.17)
Pregabalin	1.22 (0.91, 1.52)*	-3.74 (-10.26, 2.79)	-0.44 (-0.86, -0.01)*

*Note: The β_1-β_5 are coefficients from the linear regression with the appropriate residual optimisation models. The coefficients are presented with their 95% confidence intervals (95% CI). * Represents a P-value lower than 0.05.*

4.4.2. Impact of gabapentinoid classification on opioid prescribing

Despite some fluctuations, the monthly prescribing trend of opioids in English primary care decreased from 1,031.0 to 921.9 DDD/1000 registrants/month from April 2013 to May 2021. The proportional decrease was higher for strong opioids (81.0 DDD/1000 registrants/month; 19.2%) than for weak opioids (28.1 DDD/1000 registrants/month; 4.6%). Drugs for managing opioid dependence and tramadol also showed a decreased prescribing rate over the study time (Figure 4-5).

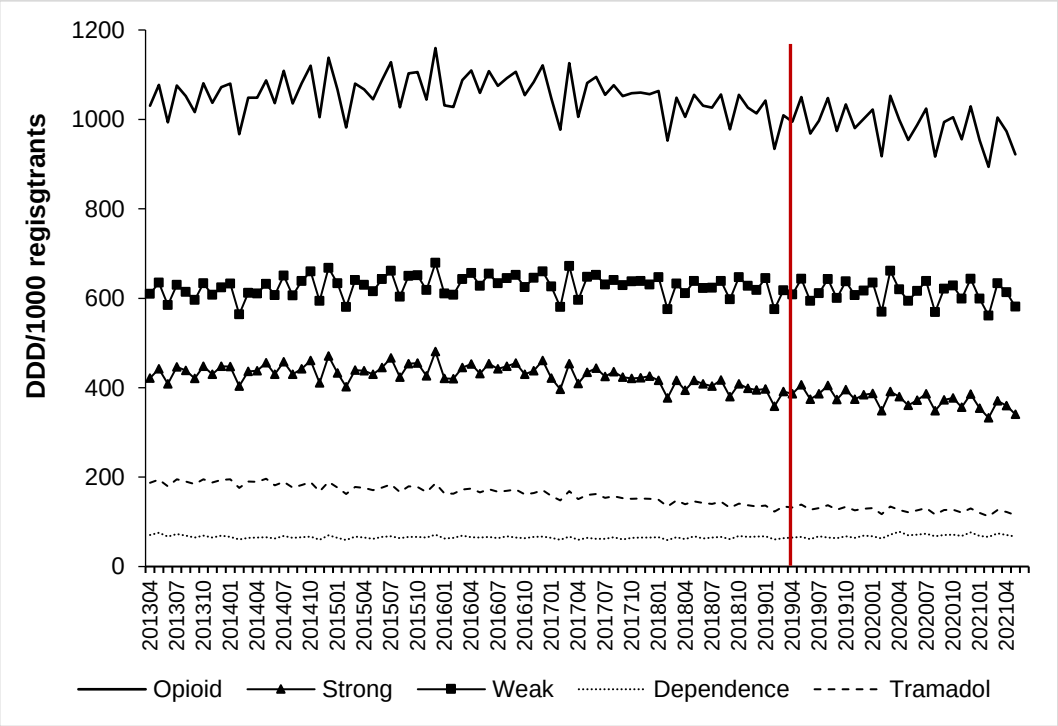


Figure 4-5. Monthly opioid prescribing in general practices in England from April 2013 to May 2021

Note: the solid red vertical line marks the classification of gabapentinoids in April 2019. Opioid dependence therapy drugs were not included in the overall amount of opioids.

The gabapentinoid classification in April 2019 had no significant impact on the level and trend of monthly prescribing rate for all opioids and for weak opioids. The prescribing of strong opioids was significantly reduced after the gabapentinoids classification in both level (β_2: -14.09, 95% CI: -27.99, -0.19; P=0.047) and trend (β_3:

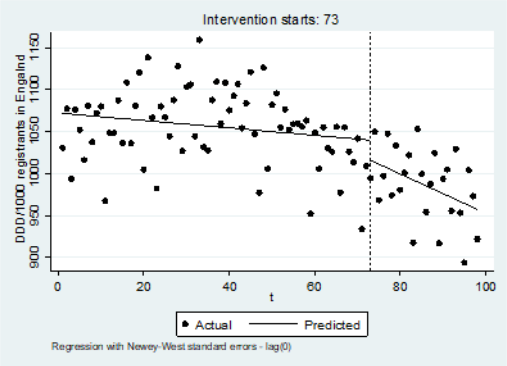
-1.04, 95% CI: -1.80, -0.28; P=0.008), though the trend was already decreasing before the intervention (β_1: -0.58, 95% CI: -0.81, -0.34; P<0.001) (Table 4-3, Figure 4-6).

Despite the decrease in strong opioid prescribing after the gabapentinoid classification, the prescribing trend for drugs for opioid dependence increased after the intervention (β_3: 0.32, 95% CI: 0.15, 0.49; P<0.001), compared to a significantly decreasing trend before the intervention (β_1: -0.05, 95% CI: -0.09, -0.01; P=0.009). Similarly, the prescribing trend of tramadol slightly increased after the classification policy (β_3: 0.27, 95% CI: 0.01, 0.53; P=0.043) (Table 4-3).

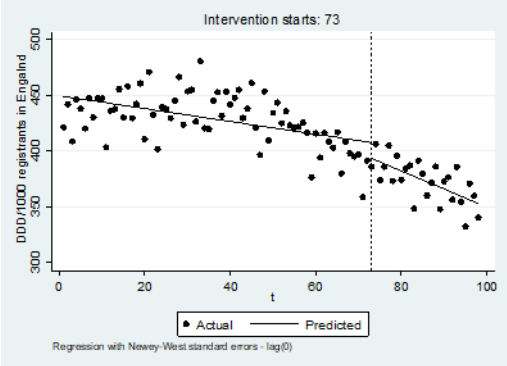
Table 4-3. The impact of gabapentinoids classification in April 2019 on opioid prescribing from April 2013 to May 2021

	Trend in pre-policy period (β_1)	**Policy impact on level (β_2)**	**Trend change in post-policy period (β_3)**
All opioids	-0.44 (-0.93, 0.04)	-24.11 (-57.38, 9.15)	-1.89 (-3.87, 0.01)
Strong opioids	-0.58 (-0.81, -0.34)*	-14.09 (-27.99, -0.19)*	-1.04 (-1.80, -0.28)*
Weak opioids	0.13 (-0.07, 0.33)	-10.38 (-26.36, 5.39)	-0.79 (-1.74, 0.16)
Dependence	-0.05 (-0.09, - 0.01)*	1.94 (-0.63, 4.52)	0.32 (0.15, 0.49)*
Tramadol	-0.85 (-0.93, -0.77)*	-2.15 (-6.78, 2.47)	0.27 (0.01, 0.53)*

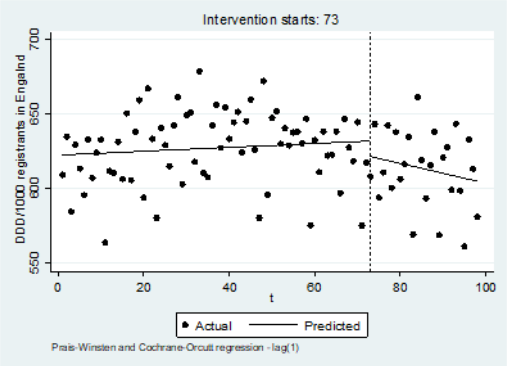
*Note: (1) The β_1, β_2 and β_3 are coefficients from the linear regression with the appropriate residual optimisation models. (2) The coefficients are presented with their 95% confidence interval (95% CI). (3) * Represents a P-value lower than 0.05.*



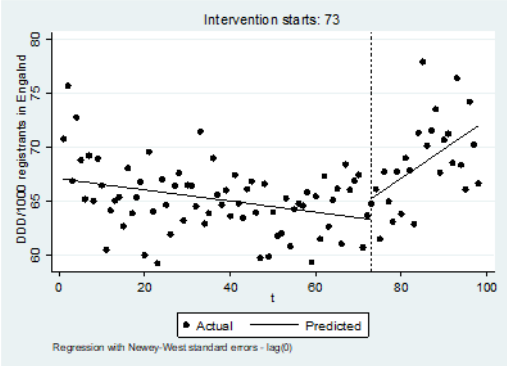
(a) Opioids



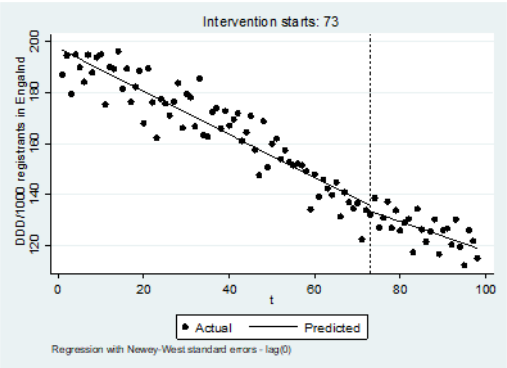
(b) Strong opioids



(c) Weak opioids



(d) Drugs for opioid dependence



(e) Tramadol

Figure 4-6. Monthly opioid prescribing before and after gabapentinoid classification in April 2019

Note: (1) the x-axis is the number of months from April 2013 (1) to May 2021 (98); (2) the vertical dotted line marks the time point of the gabapentinoid classification (73)

4.4.3. Impact of gabapentinoid classification on benzodiazepine prescribing

The monthly prescribing trends of benzodiazepines in English general practices declined over the study period (Figure 4-7) for both long-acting and short-acting benzodiazepines. When categorising benzodiazepines by their indications, the proportional decrease in hypnotic benzodiazepine prescribing (by 41.6 DDD/1000 registrants/month; 36.0%) was lower than anxiolytic benzodiazepine prescribing (by 63.6 DDD/1000 registrants/month; 70.0%), while the prescribing of benzodiazepines for epilepsy increased slightly (by 1.8 DDD/1000 registrants/month, 21.6%) over the study period.

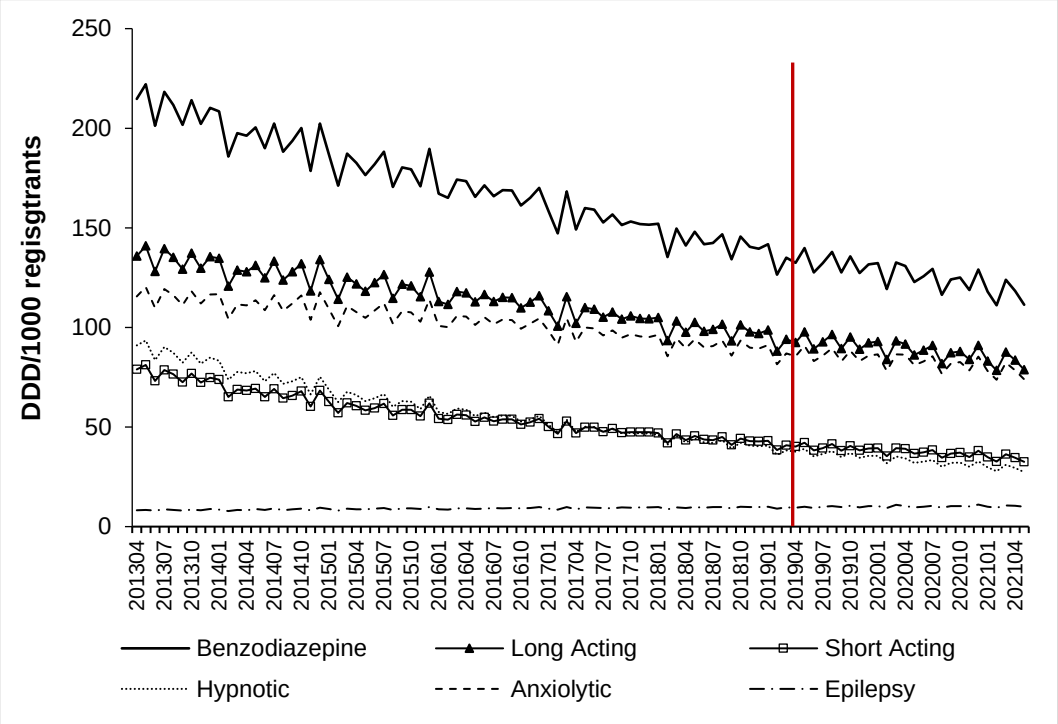


Figure 4-7. Monthly benzodiazepine prescribing in general practices in England from April 2013 to May 2021

Note: the solid red vertical line marks the classification of gabapentinoids in April 2019.

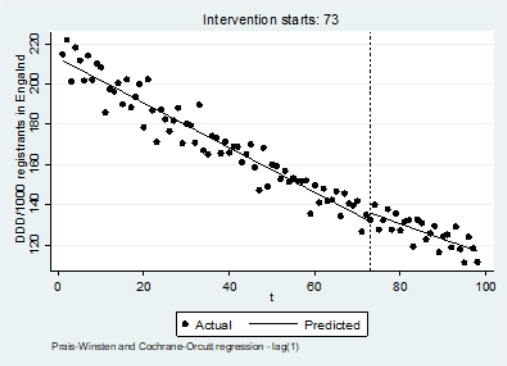
The implementation of the gabapentinoid classification policy significantly increased the level and trend of benzodiazepine prescribing after April 2019 (β_2: 4.13, 95% CI: 0.44, 7.83; P=0.029; β_3: 0.36, 95% CI: 0.14, 0.58; P=0.002), especially for short-

acting benzodiazepines (β_2: 2.97, 95% CI: 1.39, 4.54; P<0.001; β_3: 0.25; 95% CI: 0.16, 0.33; P<0.001). However, the overall trend of benzodiazepine prescribing was still decreasing after the classification (Table 4-4, Figure 4-8). When categorised by indications, the classification of gabapentinoids significantly increased both the level (β_2: 4.01; 95% CI: 2.29, 5.73; P<0.001) and trend (β_3: 0.35; 95% CI: 0.27, 0.43; P<0.001) of hypnotic benzodiazepine prescription (Table 4-4, Figure 4-8).

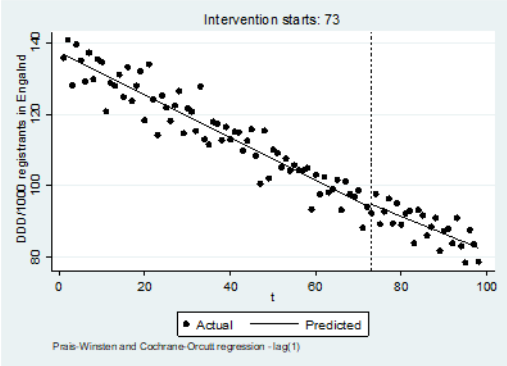
Table 4-4. The impact of gabapentinoid classification in April 2019 on benzodiazepines prescribing from April 2013 to May 2021

	Trend in pre-policy period (β_1)	**Policy impact on level (β_2)**	**Trend change in post-policy period (β_3)**
Benzodiazepines	-1.11 (-1.16, -1.07)*	4.13 (0.44, 7.83)*	0.36 (0.14, 0.58)*
Long-acting	-0.60 (-0.63, -0.57)*	1.10 (-1.17, 3.36)	0.11 (-0.02, 0.25)
Short-acting	-0.52 (-0.55, -0.48)*	2.97 (1.39, 4.54)*	0.25 (0.16, 0.33)*
Hypnotic	-0.72 (-0.76, -0.68)*	4.01 (2.29, 5.73)*	0.35 (0.27, 0.43)*
Anxiolytic	-0.42 (-0.44, -0.39)*	0.03 (-2.15, 2.20)	0.02 (-0.11, 0.15)
Epilepsy	0.02 (0.02, 0.02)*	0.00 (-0.24, 0.25)	0.00 (-0.01, 0.01)

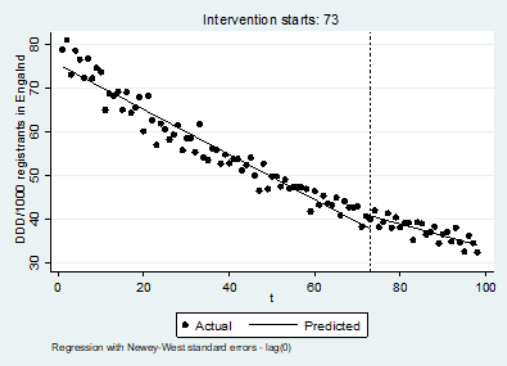
*Note: (1) The β_1, β_2 and β_3 are coefficients from the linear regression with the appropriate residual optimisation models. (2) The coefficients are presented with their 95% confidence intervals (95% CI). (3) * Represents a P-value lower than 0.05.*



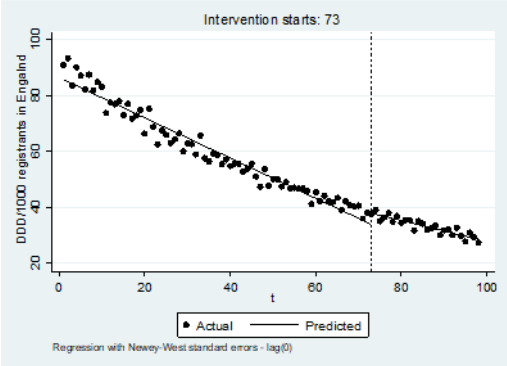
(a) Benzodiazepines



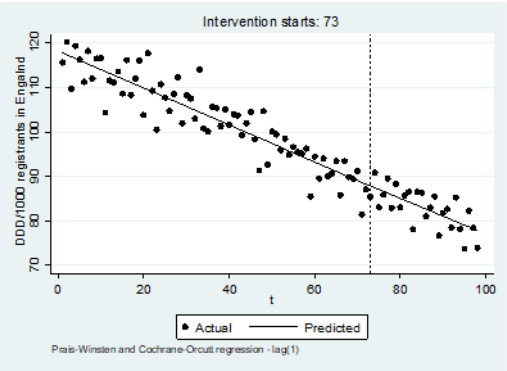
(b) Long-acting benzodiazepines



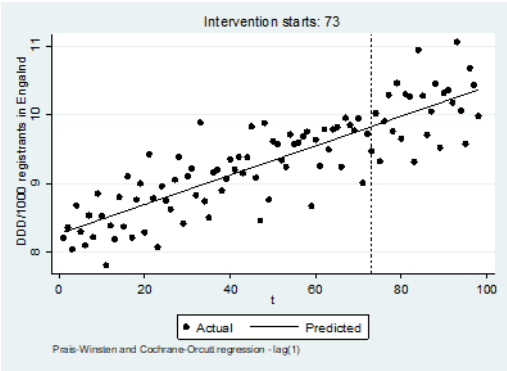
(c) Short acting benzodiazepines



(d) Hypnotic benzodiazepines



(e) Anxiolytic benzodiazepines



(f) Benzodiazepines for epilepsy

Figure 4-8. Monthly benzodiazepine prescribing before and after gabapentinoid classification in April 2019

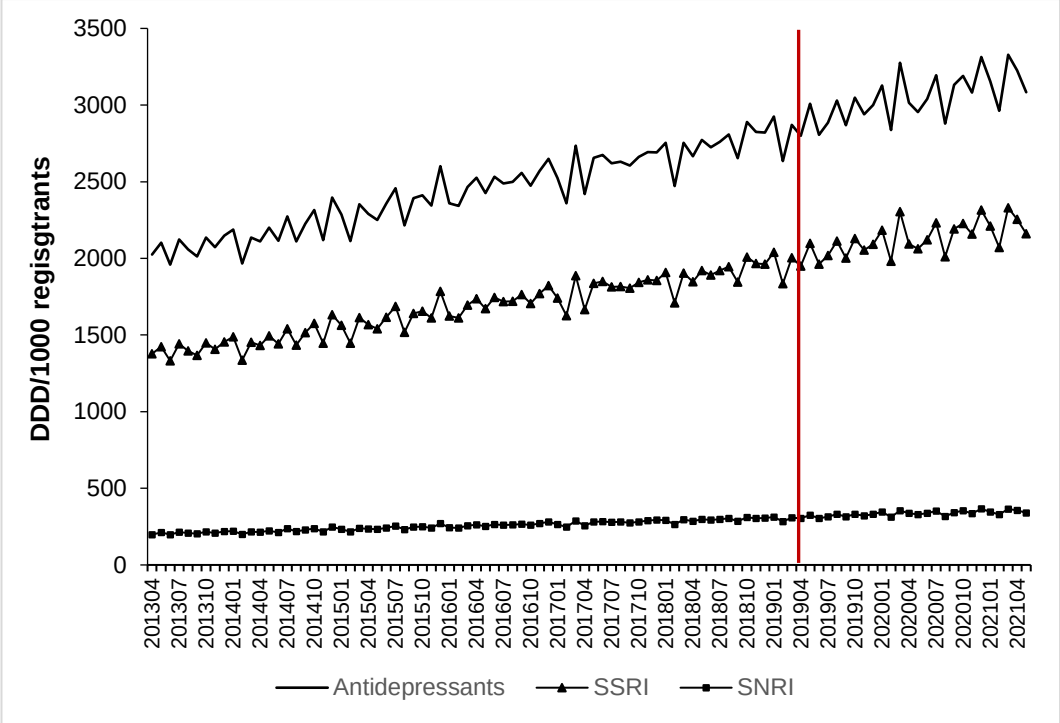
Note: (1) the x-axis is the number of months from April 2013 (1) to May 2021 (98); (2) the vertical dotted line marks the time point of the gabapentinoid classification (73)

4.4.4. Impact of gabapentinoid classification on antidepressant prescribing

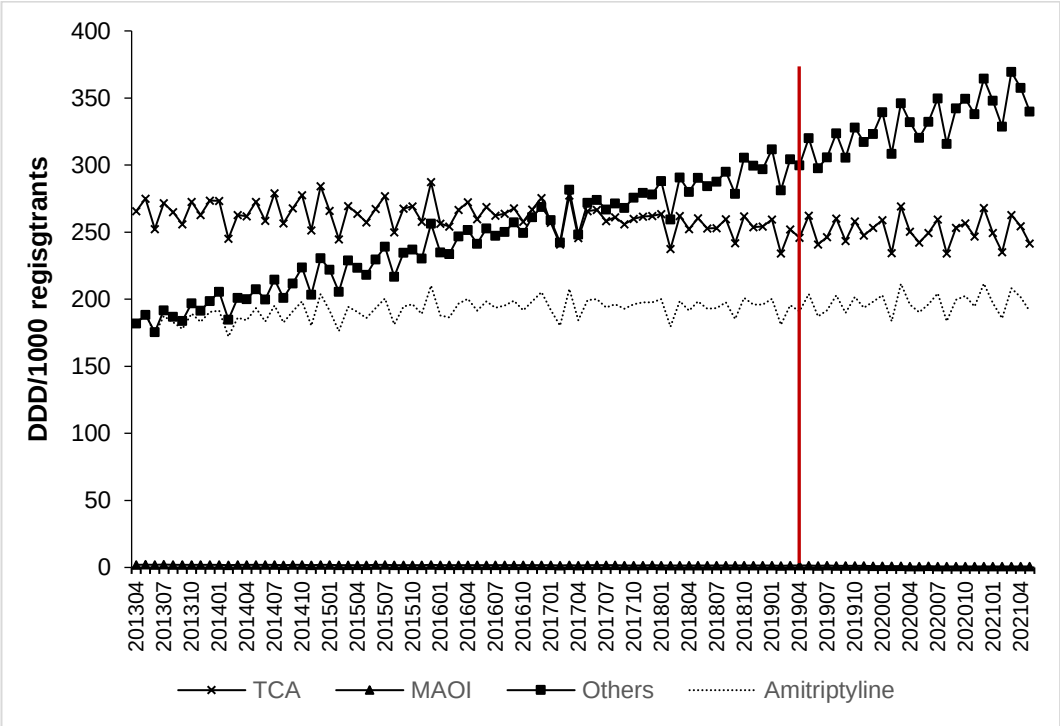
The overall prescribing trend of antidepressants in English general practices increased from 2024.8 to 3082.8 DDD/1000 registrants/month between April 2013

and May 2021 (Figure 4-9 (a)), but the trends in subgroups varied (Figure 4-9 (b)). The overall rise in the prescribing of antidepressants between April 2013 and May 2021 was mainly due to the increased prescribing of SSRIs (increased 783.4 DDD/1000 registrants/month; 56.9%) and was partially attributable to SNRIs (increased 141.88 DDD/1000 registrants/month; 71.5%) (Figure 4-9 (a)). The prescription rate of TCAs dropped slightly over the study period from 265.61 to 241.56 DDD/1000 registrants/month (dropped by 9.1%). However, the prescribing of amitriptyline, a TCA medication which is one of the first-line drug therapy for neuropathic pain [44], saw a slight increase from 182.3 to 191.05 DDD/1000 registrants/month (an increase of 4.8%) (Figure 4-9 (b)).

The classification of gabapentinoids did not significantly influence the prescribing level (i.e. level change) of antidepressants or their subgroups (Figure 4-10, Table 4-5). The ITSA results showed a small but significant decrease in the trend of prescribing MAOIs after the gabapentinoid classification (β_3: -0.02; 95% CI: -0.02, -0.01; P<0.001). The prescribing of amitriptyline was not influenced by the gabapentinoid classification (Figure 4-10, Table 4-5).



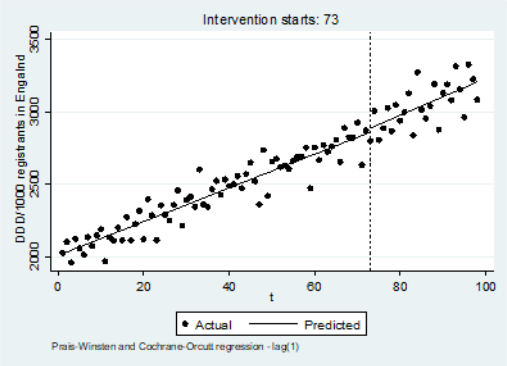
(a)



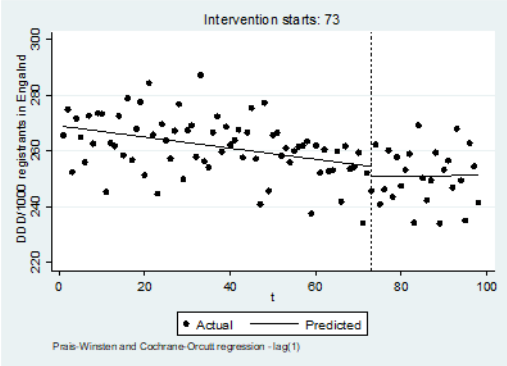
(b)

Figure 4-9. Monthly antidepressant prescribing in general practices in England from April 2013 to May 2021

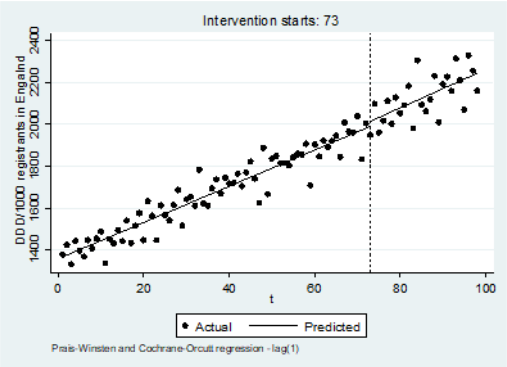
Note: (1) the solid red vertical line marks the classification of gabapentinoids in April 2019; (2) The MAOI prescription rates are low and close to the X-axis.



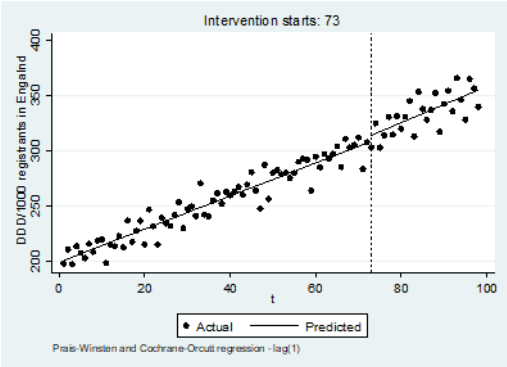
(a) Antidepressants



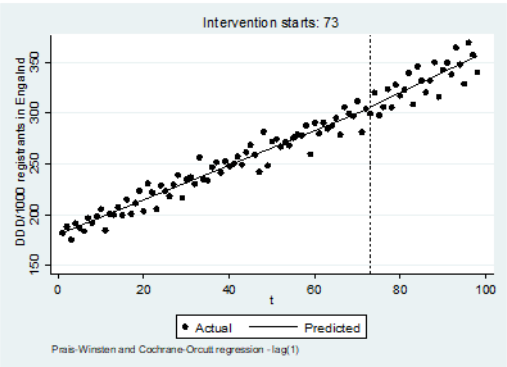
(b) TCAs



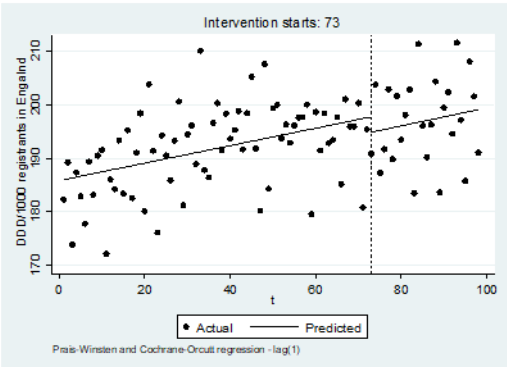
(c) SSRIs



(d) SNRIs



(e) Others



(f) Amitriptyline

Figure 4-10. Monthly antidepressant prescribing before and after gabapentinoid classification in April 2019

Note: (1) the x-axis is the number of months from April 2013 (1) to May 2020 (98); (2) the vertical dotted line marks the time point of the gabapentinoid classification (73).

Table 4-5. The impact of gabapentinoid classification in April 2019 on antidepressants prescribed from April 2013 to May 2021

	Trend in pre-policy period (β_1)	**Policy impact on level (β_2)**	**Trend change in post-policy period (β_3)**
Antidepressants	11.65 (11.00, 12.30)*	27.69 (-24.71, 80.10)	1.14 (-1.98, 4.26)
TCAs	-0.20 (-0.27, -0.13)*	-3.62 (-9.44, 2.20)	0.22 (-0.13, 0.56)
MAOIs	-0.01 (-0.01, -0.01)*	-0.06 (-0.13, 0.01)	-0.02 (-0.02, -0.01)*
SSRIs	8.68 (8.21, 9.12)*	24.64 (-11.92, 61.21)	0.50 (-1.68, 2.68)
SNRIs	1.49 (1.42, 1.57)*	5.55 (-0.38, 11.48)	0.14 (-0.21, 0.49)
Others	1.70 (1.64, 1.77)*	1.19 (-3.91, 6.29)	0.30 (-0.01, 0.60)
Amitriptyline	0.16 (0.11, 0.22)*	-2.85 (-7.48, 1.77)	0.00 (-0.27, 0.28)

*Note: The β_1, β_2 and β_3 are coefficients from the linear regression with the appropriate residual optimisation models. The coefficients are presented with their 95% confidence intervals (95% CI). * Represents a P-value lower than 0.05.*

4.5. Discussion

This study identifies the prescribing trends of gabapentinoids, opioids, antidepressants and benzodiazepines in English primary care from April 2013 to May 2021. Compared to the increasing prescribing trend of gabapentinoids from 2013, the prescribing of opioids and benzodiazepines has decreased over time, and the prescribing trends of antidepressants vary between categories. The classification of gabapentinoids in April 2019 significantly decreased the prescribing rate of gabapentinoids at both the point of the intervention and after. The prescribing of gabapentinoids in all trajectory groups was significantly reduced after the classification, especially in the group with the highest prescribing rate. The prescribing of benzodiazepines increased after the classification policy, and the prescribing of strong opioids and tramadol declined.

The primary analysis shows a significant reducing effect of the gabapentinoid classification policy on gabapentinoid prescribing, though this effect was not fully significant in the sensitivity analyses (i.e. the effect was not significant for both the level and trend change simultaneously). The sensitivity analyses 1 and 2 both

introduced a co-intervention close to the gabapentinoid classification in time, which could obscure the effect of the classification [178]. The introduction of co-interventions reduced the number of data points for estimating the level and trend change of the gabapentinoid classification, which reduced the statistical power and obscured the effect of the classification in the sensitivity analyses. The COVID-19 lockdown in March 2020 reduced the statistical power of the trend change after the gabapentinoid classification, and the effect of the ACMD letter obscured the level reduction of the gabapentinoid classification policy. This co-intervention effect can be minimised by introducing a control group that is not influenced by the intervention in a further multiple-group ITSA [172]. Sensitivity analysis 3 shortened the study period to 24 months to achieve a balanced number of points before and after the intervention, but found the effect of the classification to be non-significant. The limited time points may not have provided sufficient calculation power to detect the prescribing change in gabapentinoids, as ITSAs are highly sensitive to the number of data points available [172, 174].

The reducing effect of the gabapentinoid classification policy was supported by a study using CPRD GOLD and Aurum data [179]. Ashworth *et al* (2023) used joint point regression to evaluate the change in gabapentin and pregabalin prescription from October 2017 to September 2019 and found a significant downward trend in prevalent gabapentin prescribing immediately after the classification [179].

The gabapentinoid classification in April 2019 did not increase the prescribing of most other pain-related medicines, except short-acting benzodiazepines and hypnotic benzodiazepines. ITSA is not the most appropriate way to investigate the substitution effect of prescribing following a policy change. For example, the increased prescribing of short-acting benzodiazepines at the classification of gabapentinoids does not necessarily all come from patients switching from

gabapentinoids. However, the findings in this ITSA may still suggest a potential switch from gabapentinoids to benzodiazepines after the classification.

The gabapentinoid classification could impact gabapentinoid prescribing through several mechanisms. It could make clinicians more cautious about initiating gabapentinoids, which would reduce the number of new gabapentinoid prescriptions [162]. This may have occurred in 2016 after the publication of the ACMD public letter among some clinicians, as shown in the sensitivity analysis. Some unnecessary use of gabapentinoids, such as taking gabapentinoids without achieving satisfactory pain relief, might be revaluated and stopped after the classification policy. This may explain the large reduction effect seen in the trajectory group with the highest gabapentinoid prescribing rate. These changes in prescribing habits that may have been prompted by the classification policy are useful in preventing gabapentinoid misuse and abuse in primary care. However, there are “side effects” of the classification policy: (1) patients face more laborious drug collection; (2) GPs have an increased workload; and (3) patients may switch to uncontrolled substitutions of gabapentinoids to avoid visiting a GP every 28 days to get a new gabapentinoid prescription, which may not provide similarly effective pain relief [162]. The health service system should be aware of these potential downsides of the classification policy, and interventions could be considered to mitigate them.

The prescribing of gabapentinoids remained high after the classification policy took effect, which shows a large demand for gabapentinoids in English primary care but also indicates there is a continued risk of misuse and abuse. Gabapentinoids are now an important treatment choice for chronic pain, especially neuropathic pain [44], so the appropriate use of gabapentinoids for pain management should not be discouraged by the classification policy. However, inappropriate use of

gabapentinoids, such as off-label use without fully considering the benefits and risks, should be carefully reviewed as they might lead to gabapentinoid misuse and abuse.

According to the prescription rates and the pre-policy trends found in this study, pregabalin was prescribed more than gabapentin in English primary care from May 2014. Pregabalin has a steeper dose-response relationship than gabapentin [21], which may provide quicker pain relief but also a stronger euphoric effect and potentially a higher risk of misuse and abuse [118, 119]. In the US, only pregabalin is controlled at the national level [95]. Therefore, more attention on the misuse and abuse potential is needed in pregabalin prescribing.

The motivation for introducing the drug control policy for gabapentinoids was to reduce the misuse and abuse of gabapentinoids, which has been discussed frequently in recent years [102, 112, 160, 180]. The reduced gabapentinoid prescribing after the classification policy could reduce the diversion of gabapentinoids obtained from primary care, and therefore help reduce harm from misuse and abuse. However, the effect on reducing gabapentinoid harms could be a gradual process and may not be observed in the short term. According to the National Programme on substance abuse deaths (NPSAD), which received voluntary drug-related death reports from around 80% of coroners in England, the number of drug-related deaths involving gabapentinoids increased from 2004 to 2020, and the proportion increased from 8.9% in 2014 to 32.3% in 2020 [108]. The number of cases continued to increase in 2021 (from 118 in 2020 to 133 in 2021) according to the ONS report: *deaths related to drug poisoning in England and Wales* [181]. According to the NPSAD study, the rate of illicitly obtained gabapentinoids identified in cases of drug-related death is high and increasing over

time [108]. Therefore, policies regarding the illicit drug market are needed in addition to the national classification policy to reduce gabapentinoid harms.

This is the first study to evaluate the impact of the gabapentinoid classification on the prescribing of gabapentinoids and other pain-related drugs. This study used the national prescribing database which covers all GP practices in England and applied a population-adjusted prescribing rate, so the prescribing trends generated in this study are reliable. This study used ITSA, which is an appropriate method as the data is not seasonal and has no strong lag effect. The co-interventions of the ACMD public letter and the COVID-19 lockdown were considered in sensitivity analyses to test the robustness of the results. The prescribing of other pain medications was also evaluated using the ITSA to explore any potential substitution effects.

However, there are limitations to this study. Firstly, this study used the primary care prescribing database only, which does not include the prescribing of gabapentinoids in secondary care, private healthcare, or special settings such as prisons. Although the prescribing outside NHS primary care is assumed to be minimal, the results of this study should not be extrapolated. Secondly, this study used aggregated-level data that does not support the identification of individual gabapentinoid users. Therefore, the hypotheses about reductions in new gabapentinoid prescriptions, discontinuation of unnecessary gabapentinoid prescriptions, and substitution of gabapentinoids with benzodiazepines could not be tested. Thirdly, the impact of the gabapentinoid classification was evaluated on primary care prescribing rather than on the number of misuse and abuse cases, so no link between the classification policy and the reduction of gabapentinoid misuse and abuse can be drawn.

This chapter shows that the gabapentinoid classification policy successfully reduced the prescribing of gabapentinoids in English primary care, possibly indicating more

cautious initiation of gabapentinoids and discontinuation of some unnecessary prescribing. The classification policy achieved the largest reduction in gabapentinoid prescribing in GP practices with the highest prescribing rate of gabapentinoids over the past decade. These GP practices were mostly located in the north of England, suggesting future specialised regional policy could be efficient in optimising gabapentinoid prescribing. Further studies are needed to investigate the risks associated with gabapentinoids that could inform future policies.

Chapter 5. Data source and cohort identification

5.1. Introduction

This overarching chapter depicts the data sources, code lists and the definitions and identification of the study cohort, including the selection and justification of the database and the code lists for variables relevant to the study design. The previous two chapters (Chapter 3 and Chapter 4) have suggested the limitations of aggregate-level data in investigating the safety of gabapentinoids and the need for individual-level data. Therefore, a patient-level data source that contains a sufficient number of gabapentinoid users with CNCP and provides patient information on clinical diagnosis and drug therapy is required to enable the following chapters. Meanwhile, code lists for disease diagnoses and drug products relevant to the study questions are crucial for data extraction. In addition, the population with CNCP was extracted from the selected database as a preliminary study population in this chapter. Study cohorts and designs proposed for the following studies as in the proposal submitted for data access are also outlined to draw a clear research framework and show the cohort links between studies.

5.2. Aim and objectives

This chapter aimed to identify the databases, code lists and the population with CNCP that are frequently referenced in the following chapters. The objectives are:

(1) To describe and justify the selection of patient-level databases for the proposed studies;
(2) To develop code lists for diseases and drugs that were considered covariates in the following studies;
(3) To identify the population with CNCP from the selected patient-level database;

(4) To outline the study cohorts and designs in the following four chapters.

5.3. Databases

The individual patient data in this project was extracted from the Clinical Practice Research Datalink (CPRD), a UK primary care database that provides up-to-standard data for over 18 million UK patients from 1987 to the present [182]. CPRD data is linkable to external databases to access patients' health information outside primary care. The external databases selected in this project were the Hospital Episode Statistics Admitted Patient Care (HES APC), the Office for National Statistics (ONS) Death Registration and the ONS Small Area Level data (Table 5-1).

In the UK, primary care practices are the first point of contact for patients in the healthcare system [183]. Consultations with a general practitioner (GP) in primary care are recorded in various electronic medical recording systems [184]. Therefore, primary care databases can provide sufficient detailed information for epidemiological research, especially for chronic diseases like CNCP. CPRD was selected over the UK Biobank, the Secure Anonymised Information Linkage Databank (SAIL) databank (England and Wales), databases maintained by Public Health Scotland, and Salford Integrated Record after considering the sample size, duration, accessibility, and usability of the information of the data.

Table 5-1. Sources of data used in this study

Database	Available duration	Information retrieved
CPRD GOLD	January 1987 to December 2019	Demographics, disease history, prescriptions
CPRD Aurum	January 1995 to December 2019	Demographics, disease history, prescriptions
HES APC	April 1997 to December 2019	Events of fracture, suicide hospitalisation
ONS Death Registration	January 1998 to December 2019	Events of drug-related death and suicide death
ONS Small area level data	2015 English Index of Multiple Deprivation (IMD)	Patient-level and practice-level IMD decile

Note: CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; APC: Admitted Patient Care; ONS: Office for National Statistics; IMD: Index of Multiple Deprivation

5.3.1. Clinical Practice Research Datalink

CPRD is a UK primary care database collecting individual patient electronic health records from enrolled general practices that use the Vision® or EMIS® software as the documentation system in the UK [182]. The structure and coding in the two systems are different, so CPRD data are provided as separate GOLD and Aurum databases. CPRD GOLD data begins in January 1987 [185]. Aurum was released as a new database by CPRD in 2019, but the data begins in January 1995. Patients in GOLD and Aurum generally do not overlap, except for those who transferred between practices using different systems [185].

The CPRD routinely collects data from general practices that consent to participate with the CPRD, but patients in the consented practices could choose to opt-out of the data sharing agreement. Patients in the CPRD are flagged as 'acceptable for research' if they meet the quality criteria developed by the CPRD research team which excludes patients with non-continuous follow-up and patients with poor data recording that raises suspicion as to the validity of that patient’s records [182]. Similarly, practices are deemed "up to standard" (UTS) when they meet the CPRD's

data quality metric about data continuity and the criteria for death recording [182, 185]. By September 2020, GOLD obtained around 3.2 million active patients from 407 current contributing practices in the UK, while Aurum enrolled around 12.9 million active patients from 1350 current contributing practices in England [186, 187]. Overall, the CPRD covered 1900 primary care practices and included 16 million active patients in 2020 [188] (23.5% of the 2020 UK population), and is representative of the UK population in age, sex, ethnicity, and body mass index [182].

Health information in the CPRD is provided in separate data files, but these are linkable by the unique patient identification number [182]. GOLD clinical files and Aurum observation files contain disease diagnoses and other medical conditions. GOLD therapy files and Aurum drug issue files contain details of prescribed medications. Patient files in both GOLD and Aurum include patients' demographics. Other information such as symptoms, signs, referrals, immunisations, behavioural factors, and tests, were also recorded in corresponding files in CPRD.

The clinical-relevant information in the CPRD was recorded in code format such as clinical code and product code. In the files containing drug therapy information, each prescription recorded the date of prescription, product identification code, product strength, quantity prescribed and daily dose recommended by the GP [182]. In the clinical files, the date of diagnosis and medical codes were recorded. Medical code is a CPRD-unique coding system for the diagnosis, but the coding systems in the two databases are different due to the difference between the Vision® and EMIS® systems. CPRD GOLD uses the Read code system to record disease information, while CPRD Aurum used Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) code. The use of Read Version 2 codes in NHS started in 1985 and was retired in April 2016 as stated by NHS Digital [189]. Since then the clinical

coding in the NHS system was gradually shifted to SNOMED CT, which is more comprehensive and precise than Read codes [190].

Access to the anonymised individual patient data in CPRD must be applied for with a complete protocol and approved by an Independent Scientific Advisory Committee (ISAC). The application for this project was approved by ISAC in January 2020 (approval code 20_002) and approved for amendment in May 2020.

The data extracted from the CPRD and the linked external databases were saved and processed in the research data storage system held by the University of Manchester Research Data Management service, which is a secure, centrally hosted and administered data storage system. The RDS is project-specific and password-protected, so only researchers approved for the data administration of this project (as stated in the protocol) can access the data.

5.3.2. The English Index of Multiple Deprivation

The 2015 English IMD is a comprehensive local measure of deprivation in England routinely collected by the Department for Communities and Local Government [191]. The 2015 English IMD was selected as the measure of socioeconomic status in this study from a set of small area databases linkable with the CPRD (such as the Carstairs Index, the Townsend score and the Rural-Urban classification). The IMD was selected because it had the most comprehensive measure of socioeconomic status covering income, employment, education and skills, health, housing, crime, access to services, and living environment domains [191]. The IMD decile is a relative measure that ranks areas by their IMD score, a weighted measure of the domains, where 1 represents the least deprived 10% of areas, and 10 represents the most deprived 10% of areas.

5.3.3. Hospital Episode Statistics

The HES database is a data warehouse provided by NHS Digital that contains the records of patients at NHS hospitals in England [192]. The CPRD linkable HES databases included the HES Admitted Patient Care (APC), the HES Outpatient data, and the HES Accident and Emergency (A&E) databases. The HES APC was selected as the data source for identifying safety issues in this study because secondary care data is appropriate for evaluating the safety outcomes in this project and the HES APC has a more detailed diagnosis code (International Classification of Diseases, Tenth Revision (ICD-10) code) for research purposes than the HES A&E database.

The HES APC data provide the complete information of patients admitted to hospitals in England since April 1997 for elective or emergency use of hospital beds, regardless of the type of reimbursement (private or NHS) or the place of resident (in or outside England) [193]. The HES APC data includes information on hospitalisation episodes, diagnoses, procedures, and special care (augmented care, critical care, maternity care) [188, 194]. Hospitalisations in the HES APC setting refer to a complete hospital stay from admission to discharge, which can include more than one episode. An episode is a period within a hospitalisation when the patient is being cared for by one consultant using the beds of one health care provider. Patients can be transferred to another consultant and start a new episode during the same hospitalisation stay [193]. Diagnoses in the HES APC were coded in the International Classification of Diseases version 10 (ICD-10) coding frame. All diagnoses generated during a hospital stay are recorded in the *episode* sub-dataset of HES APC, which could contain diagnoses of diseases not relevant to the hospitalisation stay. The primary diagnoses for each episode, which is defined as

the first diagnosis of each episode, is recorded in the *primary diagnoses across a hospitalisation* sub-dataset of HES APC.

5.3.4. Office for National Statistics Death Registration

The CPRD is linkable to the ONS Death Registration for death outcomes. In the UK, most deaths are certified by a medical practitioner and registered to Local Registration Service within five days of death [195]. In some cases, deaths are referred to a coroner to investigate for more information and are not recorded within five days. In 2020, 99.3% of the 607,922 deaths in England and Wales were registered within one year [196]. The ONS Death Registration collects registered death data and provides the date and causes of death (up to 15 causes for each death) since 2 January 1998 in England and Wales. The cause of death is recorded using ICD-10 codes in the ONS Death Registration, where drug-related death and suicide death both have corresponding ICD-10 codes [197].

5.4. Code list developments

5.4.1. Disease code lists

The disease code lists in this project are used to identify the study population, identify baseline comorbidities, and measure the Charlson Comorbidity Index of patients from the CPRD.

Code lists for identifying chronic pain in the CPRD

The available code lists for identifying chronic pain in the CPRD vary across studies, and no existing code list from online clinical code repositories can be directly used for this study. Therefore, code lists for chronic pain were developed for both CPRD GOLD and Aurum to identify patients with chronic pain in the CPRD. According to a

systematic review of chronic pain definitions in epidemiological studies, the duration of chronic pain is defined inconsistently in epidemiological studies, but pain over three months was the most common criterion for chronic pain [198]. Similarly, the International Association for the Study of Pain (IASP) defined chronic pain as "persistent or recurrent pain lasting longer than three months" [1]. Therefore, chronic pain in this project is defined as adult patients with a diagnosis (i.e. a Medical code in CPRD GOLD or Aurum databases) indicating a potential of having or developing a pain condition that lasts over three months.

The development of the chronic pain code lists has three steps (Figure 5-1). Firstly, existing CPRD code lists for pain conditions were identified from the literature. An existing Read code list for chronic pain developed by GPs in collaboration with the University of Nottingham provides 591 Read codes covering a range of conditions including arthritis, low back pain, neuropathic pain, and fibromyalgia. Another eight Read code lists for five pain conditions (Table 5-2) were identified from the Clinical Codes, an Online Clinical Codes Repository providing over 521 code lists for the CPRD and other Electronic Medical Records systems [199]. Among the eight Read code lists, three osteoarthritis code lists were the same, which means the three studies used the same code list for osteoarthritis. The two Read code lists for rheumatoid arthritis had 48 overlaps. After combining all of the code lists and removing duplicates, Clinical Codes provided 389 Read codes for chronic pain, of which only 180 matched the 591 codes developed by GPs in Nottingham. The low overlap rate of the code lists suggested the necessity of a new search of the clinical codes using keywords for chronic pain.

Secondly, a list of keywords based on the researcher's knowledge was applied to the CPRD code browser to identify the potential codes of chronic pain (Appendix 3).

The existing code lists identified in step one were added to the potential code list of chronic pain.

Thirdly, the potential code list was screened by four reviewers to form the final code list for chronic pain. The reviewers are experienced in using CPRD to research chronic pain and opioid prescribing. The code list obtained diseases and symptoms that are very likely to develop long-term pain, including neuropathic pain, rheumatoid arthritis, arthritis, osteoarthritis, low back pain, fibromyalgia, and a range of other conditions [200], as well as symptoms, such as pain and ache (Appendix 3). When there was disagreement among the reviewers, consensus was reached after the discussion focused on the potential duration of the diagnoses or symptoms, specifically whether they could last for over three months. There were 1099 and 1413 medical codes identified from CPRD GOLD and Aurum, respectively.

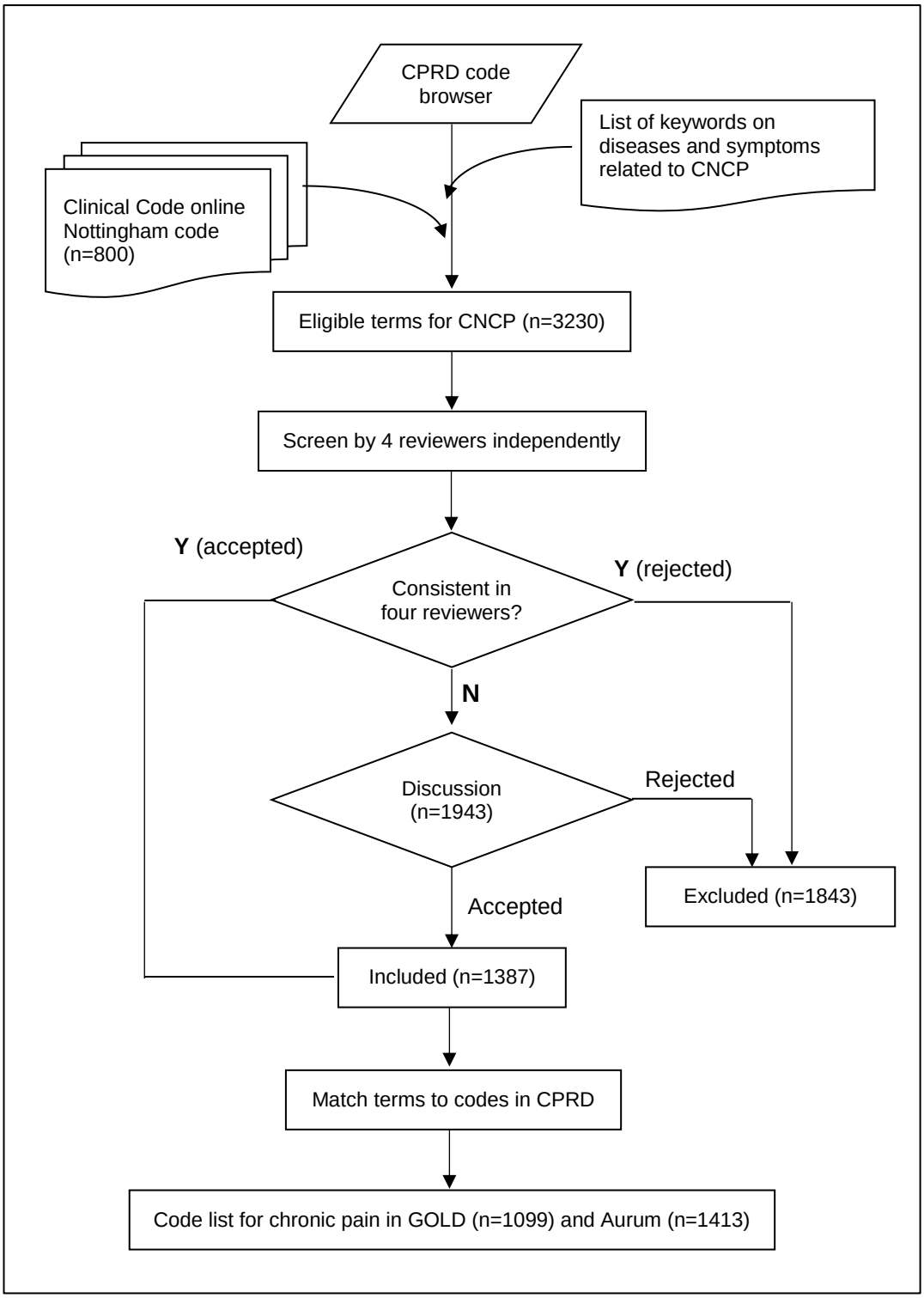


Figure 5-1. Flow chart for the development of the code list for chronic pain

Table 5-2. Literature source for chronic pain codes lists on online clinical code repository

Author	Title	Read code	Items
Doran *et al.*, 2011 [201]	Effect of financial incentives on incentivised and non-incentivised clinical activities: a longitudinal analysis of data from the UK Quality and Outcomes Framework	Back pain	117
Nicholson *et al.*, 2013 [202]	Optimising Use of electronic health records to describe the presentation of rheumatoid arthritis in primary care: a strategy for developing code lists	Rheumatoid Arthritis	61
Reilly *et al.*, 2015 [203]	Inequalities in physical comorbidity: A longitudinal comparative observational study of people with severe mental illness in the UK	Osteoarthritis	128
		Rheumatoid Arthritis	54
Kontopantelis *et al*., 2015 [204]	Primary care consultation rates among people with and without severe mental illness: a UK cohort study using the Clinical Practice Research Datalink	Osteoarthritis	128
Kontopantelis *et al.*, 2015 [205]	Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study	Osteoarthritis	128
Gorton *et al.*, 2018 [206]	Risk of unnatural mortality in people with epilepsy	Migraine	29
		Neuropathic pain	24

Cost lists for identifying cancer in the CPRD

Cancer code lists were required for excluding cancer patients from the chronic pain population. Keywords for generating the code lists for cancer were generated by a group of researchers at the University of Manchester with consultation from clinicians in Christie NHS Foundation Trust (Manchester). The keywords were searched in CPRD code browsers to generate the code lists for cancer. The cancer pain code lists include 1,955 Read codes for CPRD GOLD and 2,370 SNOMED CT codes for CPRD Aurum.

Code lists for identifying comorbidities in the CPRD

Code lists for comorbidities relevant to gabapentinoid safety and that often co-exist with chronic pain are prepared in this chapter for further studies. Most diseases Read code lists for CPRD GOLD were referenced from the Cambridge@CPRD

research group [207] (Table 5-3). This research group under the Cambridge University Department of Public Health and Primary Care developed 37 code lists for CPRD GOLD in 2018 to identify long-term conditions from Electronic Health Record (EHR) databases. Each code list was checked by at least two clinicians [207]. The read codes for chronic kidney disease (CKD) from Cambridge@CPRD require additional values of estimated glomerular filtration rate from the clinical file, which needs extra data extraction from CPRD and therefore was not adapted in this project. The CKD code list used in this project was referenced from a 2015 study with its code lists published on ClinicalCodes.org, an online clinical codes repository to improve the validity and reproducibility of medical database research [203]. Disease lists for rheumatoid arthritis and osteoporosis were not included in the Cambridge@CPRD project, therefore the relevant read code lists published on the London School of Hygiene & Tropical Medicine (LSHTM) Data Compass [208], a curated digital repository of research outputs produced with involvement by staff and students at LSHTM, were extracted for use. Read code lists from the LSHTM Data compass for rheumatoid arthritis and osteoporosis were most recently updated in December 2018.

Since CPRD Aurum was launched in 2017 [185] and was not fully functional until 2019, there have not been many studies published using this database, nor did Cambridge@CPRD create any medical code lists, so medical code lists for diseases in Aurum could not be easily referenced. Also, inconsistency in disease definition between research groups is common. If the code lists for the same disease were obtained from two resources (i.e. two published studies) to identify the disease from GOLD and Aurum separately, the inconsistency in definition might cause bias and leave the results from the two databases incomparable. An ideal way to generate the Aurum disease list would be to

apply the criteria and algorithm used for code generation in GOLD to Aurum. However, the GOLD disease code lists used in this project were referenced from published sources, and the process for generating the code lists was not available. Therefore, a matching of the medical code list from CPRD GOLD to CPRD Aurum was conducted using the NHS Data Migration tool released in April 2020 [209].

The medical codes in CPRD Aurum are recorded using the SNOMED CT coding system, a concept-based multi-hierarchical ontology where concepts can be related to each other [210]. The Aurum disease code system includes three important variables: medical code, SNOMED CT concept ID and SNOMED CT description ID.

The NHS Data Migration tool is a mapping file matching Read code to SNOMED CT concept code to support a smooth nationwide transition from the READ code system to the SNOMED CT system in the NHS [209]. However, with the nature of a concept-based coding system in SNOMED CT, the mapping from Read code to SNOMED CT code cannot be completely precise because one read code sometimes has multiple SNOMED CT description ID matches and one SNOMED CT description ID can match more than one read code. Therefore, each Read code was matched to both a SNOMED CT concept ID and SNOMED CT description ID to increase matching accuracy. Then the matched SNOMED CT concept ID and SNOMED CT description ID were used to identify the corresponding medical code in the CPRD Aurum code browser data file. The finalised medical code lists were screened manually to exclude diseases that

were not included in the original GOLD code list of the disease but fell under the same SNOMED CT concept (Table 5-3).

Table 5-3. Disease code lists and number of medical codes

Disease	Source	CPRD GOLD (n)	Matched CPRD Aurum (n)
Alcohol problem	CPRD@Cambridge [207]	54	80
Anxiety	CPRD@Cambridge [207]	197	299
CKD	ClincalCode.org [203]	74	88
COPD	CPRD@Cambridge [207]	54	63
Depression	CPRD@Cambridge [207]	124	129
Diabetes	CPRD@Cambridge [207]	319	432
Epilepsy	CPRD@Cambridge [207]	119	139
Psychoactive substance misuse	CPRD@Cambridge [207]	282	352
Rheumatoid arthritis	LSHTM Data Compass [208]	56	69
Osteoporosis	LSHTM Data Compass [208]	81	81

* CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease

Code lists and calculation of the Charlson Comorbidity Index

The Charlson Comorbidity Index is a commonly used comorbidity scoring system in epidemiological studies that can help predict mortality and evaluate a patient's general health condition [211]. An optimised Charlson Comorbidity Index (CCI) was adapted to measure the general health condition of the patients in this project (Table 5-4). It grouped and weighted 17 clinically relevant comorbidities to assign a CCI score to the patient [211, 212]. The Read-code lists for the comorbidities in the CCI were referenced from the methodology paper that adapted and validated the Charlson Index for Read-coded databases [212]. The CCI comorbidity disease code lists in Aurum were generated using the mapping strategy mentioned in the Comorbidities section.

Table 5-4. Optimised Charlson Comorbidity Index

Category	Weight
AIDS	6
Cancer	2
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart disease	1
Dementia	1
Diabetes	1
Diabetes with complications	2
Hemiplegia	2
Metastatic tumour	6
Mild liver disease	1
Moderate liver disease	3
Myocardial infarction	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Renal disease	2
Rheumatological disease	1

Note: AIDS: Acquired Immune Deficiency Syndrome

5.4.2. Product code lists

The product code lists for the gabapentinoids and other drugs proposed to be relevant to the safety of gabapentinoids (gabapentinoids, opioids, benzodiazepines, antidepressants, and Z-drugs) were searched using the CPRD code browser. Names of chemical substances under the drug category defined in Chapter 4 (Section 4.3.3) were applied as keywords in the drug substance name search in the CPRD code browser. All formulations of the identified drugs were included in the product code lists (Table 5-5).

Table 5-5. Medicine code lists and number of product codes

Disease	CPRD GOLD (n)	CPRD Aurum (n)
Gabapentinoids	197	87
Opioids	1683	886
Benzodiazepines	379	99
Antidepressants	952	366
Z-drugs	61	18

5.4.3. Code lists for potential adverse events related to gabapentinoids

The safety outcomes proposed to be studied in the following chapters are the serious adverse events of drug-related death, suicide, and fracture hospitalisations. These were selected due to their severity and frequency. The definition of the serious adverse events and the code-generating process are described below.

Codes to identify drug-related death from the ONS death registration

Drug-related death is defined as death related to drug poisoning [217]. It includes accidents, suicides and assault deaths involving drug poisoning and poisoning deaths from drug abuse and dependence. The drug-related death defined in this study excludes other adverse effects of drugs (e.g., allergy). The ICD-10 code list for drug-related deaths was referenced from the ONS quality and methodology report for deaths related to drug poisoning in England and Wales (Table 5-6) [213].

Table 5-6. International Classification of Diseases, Tenth Revision (ICD-10) codes used to define deaths related to drug poisoning

Description	ICD-10 Codes
Mental and behavioural disorders due to drug use (excluding alcohol and tobacco)	F11–F16, F18–F19
Accidental poisoning by drugs, medicaments and biological substances	X40–X44
Intentional self-poisoning by drugs, medicaments and biological substances	X60–X64
Assault by drugs, medicaments and biological substances	X85
Poisoning by drugs, medicaments and biological substances, undetermined intent	Y10–Y14

Codes to identify fracture hospitalisation from the HES APC data

Fracture in this study was defined as a fracture in any body region caused by an external power. Fractures relevant to gabapentinoids are usually caused by falls following gabapentinoids' dizziness side effects [8]. Therefore, fractures caused by pathological reasons, such as fatigue, stress, and pathological fractures, were excluded. Hospitalisations with a ‘primary diagnosis’ (first diagnosis recorded during each episode of care in a spell) of fractures in gabapentinoid users and non-users were identified by ICD-10 codes from the HES APC database. The ICD-10 code list for fracture referenced a published study about the risk of fracture in opioid users [214] (Appendix 4).

Codes to identify suicide death and hospitalisation from the HES APC and ONS death registration

Suicide is defined as a composite outcome of suicide death (fatal suicide attempt) and suicide hospitalisation (non-fatal suicide attempt) in this study. The definition of fatal suicide attempt and non-fatal suicide attempt were referenced from the US National Institute of Mental Health (NIMH) which states fatal suicide attempt as “*death caused by self-directed injurious behaviour with intent to die as a result of the behaviour*”, and non-fatal suicide attempt as “*a non-fatal, self-directed, potentially*

injurious behaviour with intent to die as a result of the behaviour" [215]. However, since the intention of self-harm is difficult to distinguish in the ICD-10 code, self-harm diagnoses regardless of intention were included in the suicide code list. Not specifying the intention of self-harm was supported by the self-harm definition in the NICE guideline that "intentional self-poisoning or injury, irrespective of the apparent purpose" [216]. The ICD-10 main codes for suicide were referenced from the US national health statistics report about the ICD-10 code for non-fatal suicide attempts and intentional self-harm (Table 5-7) [217].

Table 5-7. International Classification of Diseases, Tenth Revision (ICD-10) codes used to define suicide

Category	**ICD-10 Codes**
Suicide attempt	T14.91
Poisoning by drugs, medications and biological substances	T36-T50
Toxic effects of nonmedical substances	T51-T65
Asphyxiation, suffocation, hanging	T71
Intentional self-harm	X71-X83

5.5. Cohort identification

Since the following studies (Chapters 6-9) using the patient-level database are all about the use of gabapentinoids in patients with CNCP, the group of patients with CNCP is required as a preliminary study population. Study cohorts proposed for the following studies, such as gabapentinoid users with CNCP and the matched gabapentinoid non-users with CNCP, are sub-cohorts embedded in the population with CNCP. Therefore, the identification of the population with CNCP and an outline of the proposed study cohorts for the subsequent chapters are described below.

5.5.1. Population with chronic non-cancer pain

The population with CNCP is defined as adult patients who had a new occurrence of CNCP between 1 January 2005 and 31 December 2019, had no history of cancer and were eligible for the CPRD external link eligible dataset. It is assumed that any chronic pain diagnosis with no other chronic pain diagnosis in the 6 months before is unrelated to any previous chronic pain condition and was defined as a new occurrence of chronic pain. Since chronic pain near the onset of cancer could be caused by cancer, pain diagnoses that occur in the 12 months before a cancer diagnosis were treated as cancer pain and excluded. Therefore, a new occurrence of CNCP is defined as a chronic pain diagnosis with no previous chronic pain diagnoses in the 6 months before and no previous cancer diagnosis in the 12 months before.

The date of the patient's first new occurrence of CNCP during the study period was defined as the *study entry date*. The patient's *study exit date* is the earliest of the following: (1) the last date of data collection from the patient's practice (2) the date that the patient left their practice (due to migration etc.), (3) the end of the study (31 December 2019), (4) the date 12 months before the patient's first cancer diagnosis if any, (5) the patient's date of death.

Patients were selected for the CNCP study population if they meet the following criteria: (1) had a new occurrence of CNCP between 1 January 2005 and 31 December 2019; (2) had at least 12 months of acceptable for research standard records before the study entry date; (3) aged more than 18 years at study entry date; (4) had no diagnosis of cancer before the study exit date; (5) eligible to external link to HES and ONS Death Registry.

The study period was set from 1 January 2005 to 31 December 2019 because pregabalin was licensed in 2004 so the earliest time to observe pregabalin users is assumed to be one year after pregabalin launched [71]. A patient's observation period is defined as the 12-month lookback period and the follow-up period. A patient's follow-up period is defined as the period from the study entry date to the study exit date (Figure 5-2). Therefore, the observation period of a patient could start as early as 1 January 2004 if the patient's study entry date was 1 January 2005.

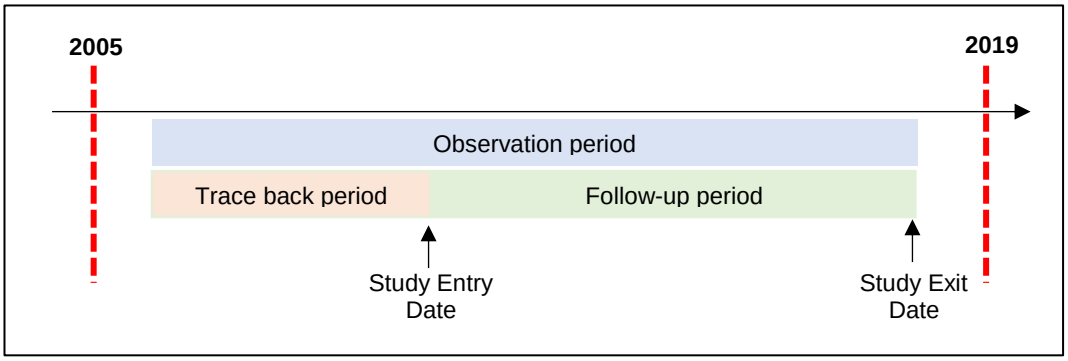


Figure 5-2. Definition of the observation and follow-up periods

Patients were identified from CPRD GOLD and Aurum using the code lists for chronic pain and cancer and the described identification criteria. The identification of the CNCP population was conducted in the CPRD cloud by the database fob holder at the University of Manchester. As the number of patients with CNCP in CPRD is large, the full data of the CNCP population was not downloaded. Instead, full patient data for the sub-cohorts in the following chapters that were actually used for data analysis were downloaded.

Overall, 10,897,483 (16.0% of the denominators) patients with CNCP in 2005-2019 were identified in the CPRD cloud. Among them, 8,267,003 have external linkage to the 2015 English IMD, HES APC and ONS Death Registration (Table 5-8).

Table 5-8. The number of patient counts in the cohort identification

	CPRD GOLD	CPRD Aurum	CPRD all
CPRD whole database (October 2020)			
Denominator	21,948,966	46,178,637	68,127,603
Acceptable for research	19,227,238	37,607,045	56,834,283
Linkable to external databases	10,948,661	40,701,418	51,650,079
Number of practices	937	1,441	2,378
CNCP cohort			
Acceptable for research	2,822,184	8,075,299	10,897,483
Linkable to external databases	1,131,536	7,135,467	8,267,003

5.5.2. Study design and cohorts in the following chapters

Two study cohorts were identified from the study population with CNCP. The main study cohort included all gabapentinoid users in the CNCP population who were prescribed at least one gabapentinoids in the follow-up time. The patients who had not been prescribed gabapentinoids during the follow-up time in the CNCP population were matched 5:1 to gabapentinoid users by age, gender and practice to form the gabapentinoid non-user cohort. Serious adverse events were identified in the two study cohorts.

Different study cohorts were selected to solve different study questions in Chapters 6 to 9 (Figure 5-3). Chapters 6 and 7 are matched cohort studies that used both gabapentinoid user and non-user cohorts to study the characteristics and the risk of serious adverse events. Chapter 8 is a cohort study that only used the gabapentinoid user cohort to investigate the utilisation pattern of gabapentinoids. Chapter 9 is a self-controlled case series study that extracted the gabapentinoid users that had fracture hospitalisations as the study cohort.

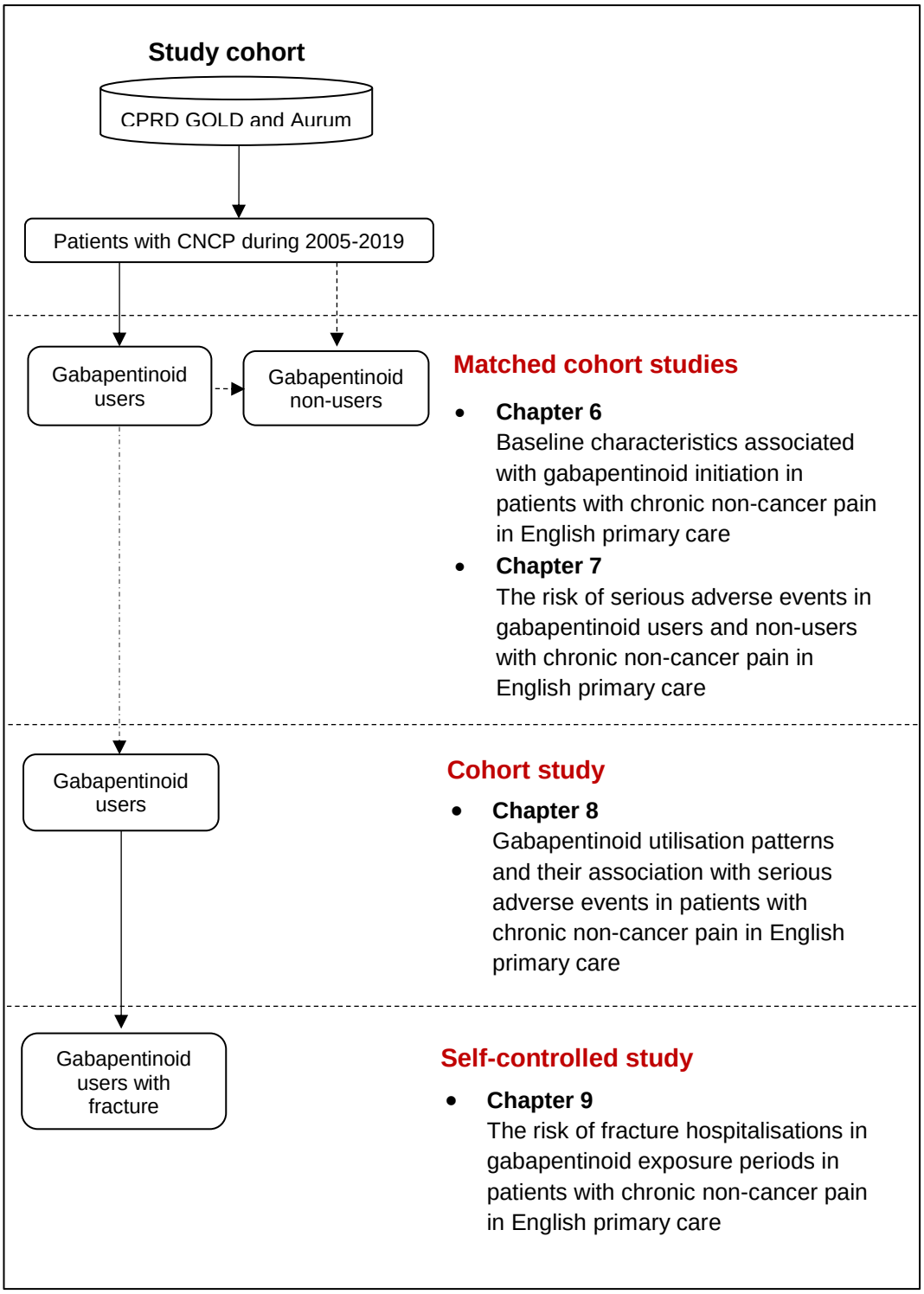


Figure 5-3. Conceptual framework of the study designs and study cohorts

Chapter 6. Baseline characteristics associated with gabapentinoid initiation in patients with chronic non-cancer pain in English primary care

6.1. Introduction

To investigate the safety of gabapentinoids, the studies using individual-level data commenced with this drug utilisation study to understand the initiation of gabapentinoids, with a focus on the characteristics of gabapentinoid users. This is because there are currently limited studies on the characteristics of gabapentinoid users in the UK.

In an observational drug utilisation study using the UK Health Improvement Network (THIN) primary care database, Asomaning *et al.* (2016) presented the characteristics of pregabalin users between September 2004 and July 2009 [89]. In the cohort of 18,951 pregabalin users identified, the median age of patients was 58 years, and 60% were female [89]. Around 13.7% of the pregabalin users were ever given a record of drug and/or alcohol abuse in the database [89]. The study also indicated a high rate of pregabalin users being prescribed concomitant medications, but the definition and measure of concomitant medications were not fully explained [89]. Asomaning *et al.*'s study was conducted 5 years after pregabalin was first launched in the UK market. With the rapid increase of pregabalin utilisation over the past decade, pregabalin users' profiles may have changed.

Another cohort study identified patients over 40 with osteoarthritis between 1995 and 2015 in the CPRD database and found that the prescribing rate of gabapentinoids was higher in women and younger patients [87]. However, the baseline characteristics including comorbidities and the use of pain-related drugs in

gabapentinoid users, especially those with chronic pain, have not been thoroughly studied.

Since gabapentinoids are indicated mainly for neuropathic pain [8], gabapentinoid users with CNCP are hypothesised to have a higher chance of neuropathic pain, relevant comorbidities, and therapies than patients who are not prescribed gabapentinoids in the CNCP population. These baseline comorbidities and drug therapies are likely to be relevant to the initiation of gabapentinoids. Nevertheless, this hypothesis has not been explored in any study comparing the baseline characteristics of gabapentinoid users with non-users in patients with CNCP.

6.2. Aim and objectives

This chapter is a hypothesis-exploring study that aims to characterise baseline pain-related medicine use and the health conditions of gabapentinoid users and non-users in the CNCP population. The results of this study are used to form further study questions about gabapentinoids safety and prepare the confounding factors to adjust in further studies. The objectives are:

(1) To describe the baseline comorbidities in gabapentinoid users and non-users in the CNCP population;
(2) To identify the baseline utilisation of pain-related medicines in gabapentinoid users and non-users in the CNCP population;
(3) To analyse factors associated with the initiation of gabapentinoids in patients with CNCP.

6.3. Methods

6.3.1. Study design and data sources

This retrospective matched cohort study investigates the differences in baseline characteristics and pain-related drug use between gabapentinoid users and non-

users with CNCP from 1 January 2005 to 31 December 2019, using the anonymised individual patient healthcare data from the CPRD, a UK primary care database [182]. The 2015 IMD deciles, indicating the socioeconomic status of the patients, from the CPRD-linked Index of Multiple Deprivation 2015 database were provided directly by CPRD. Patients were followed from the study entry date (i.e. the first CNCP diagnosis) to the 12 months after the index date (Figure 6-1).

A retrospective matched cohort study design was selected for this study because it can measure potential causes (i.e. risk factors) of outcomes when randomised controlled trials (RCTs) are not feasible, compare the characteristics between different groups of patients, and saves budget compared to prospective cohort study [218]. Matching in cohort studies reduces the required sample size and improves computational efficiency without jeopardising the statistical power of analysing the study outcomes [219]. According to a count conducted to look at the study feasibility (Appendix 2), approximately 10% of patients with CNCP were gabapentinoid users. If 90% of the CNCP population were never prescribed gabapentinoids, the resulting number of gabapentinoid non-users would be prohibitively large.

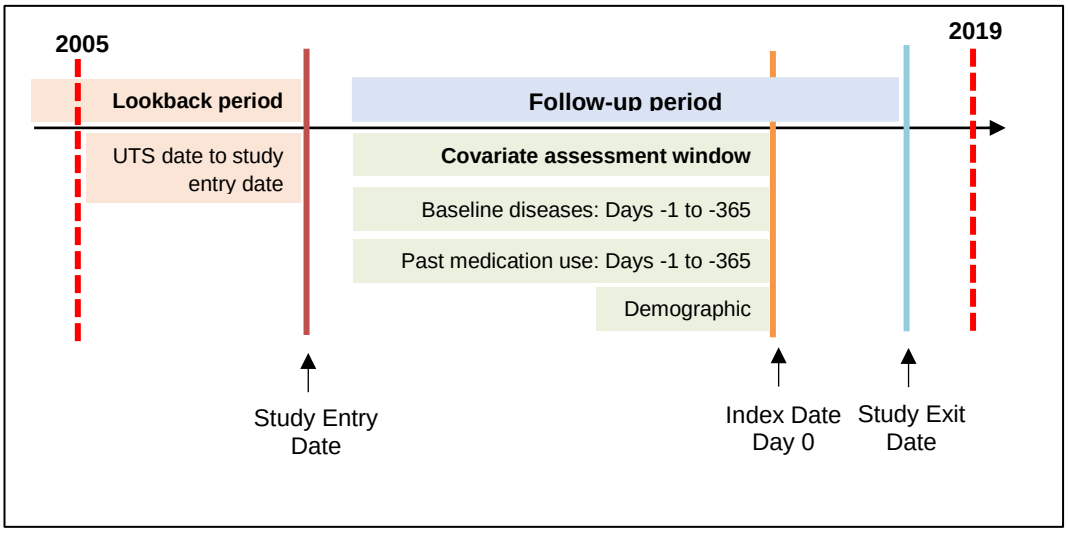


Figure 6-1. Definition of the follow-up period for the matched cohort study

6.3.2. Study population

Patients in the CNCP population (identified in Section 5.5.2, Chapter 5) that were prescribed at least one gabapentinoids during the follow-up period were defined as the cohort of *gabapentinoid user*s. Patients in the CNCP population that were not prescribed gabapentinoids were matched 5:1 to gabapentinoid users by age, gender, and practice and defined as the matched cohort of *gabapentinoid non-user*s. The *gabapentinoid non-user* cohort included some patients that would later become gabapentinoid users, in which case only time before the first gabapentinoid prescription for that patient was contributing to the gabapentinoid non-user cohort. *Gabapentinoid users* were also categorised into two subgroups: *gabapentin initiators* and *pregabalin initiators*, depending on the first gabapentinoid drug prescribed to each patient.

Gabapentinoid users in the CNCP population were identified from the CPRD GOLD therapy files and CPRD Aurum drug issue files using gabapentinoid product code lists. The date of the first gabapentinoid prescription was defined as the *index date*. Gabapentinoid non-users were identified from the population with CNCP and matched to gabapentinoid users with replacement in a ratio of 5:1 by age, gender and practice [220] on a *dummy index date*, i.e., their matched gabapentinoid user's index date.

Matching with replacement is a matching technique where one patient can be sampled repeatedly in the matched cohort [221]. Unlike case-control studies, the matching process in a matched cohort study does not have adverse effects on the effect estimation [222]. Although a matching ratio of 1:1 is frequently used in matched cohort studies, a 1:5 matching ratio was selected in this study to ensure sufficient cases and better statistical power in further studies (Chapters 7 and 8)

[221]. As this study aimed to investigate the potentially influential factors of gabapentinoid initiation, a simple matching on age, gender and practice (for other unmeasurable socioeconomic factors) was applied to avoid overmatching [223].

An eligible pool of matching candidates (i.e. gabapentinoid non-users) was selected using the following criteria:

(1) the candidate had no gabapentinoid prescription in the observation period, or the candidate's first gabapentinoid prescription occurred after the matching gabapentinoid user's index date;
(2) the candidate's first CNCP diagnosis occurred before the matched gabapentinoid user's index date (Figure 6-1);
(3) the candidate's end of follow-up time occurred after the matched gabapentinoid users' index date.

Patients in the candidate pool were selected using an exact match with the gabapentinoid users for practice and gender, and a range match for age (age must be within a 5-year difference, where the closest match to the gabapentinoid user is selected).

The gabapentinoid user cohort was divided into gabapentin initiator and pregabalin initiator subgroups to investigate the influential factors for gabapentin or pregabalin initiation. Gabapentin (pregabalin) initiator was defined as patients who were prescribed gabapentin (pregabalin) only on the index date. Patients who were prescribed both gabapentin and pregabalin on the index date were excluded from both subgroups.

6.3.3. Outcome measures

Baseline demographics and time to gabapentinoid initiation

Baseline demographics are defined as the age, gender, practice location, and socioeconomic status at the index date. Patients' years of birth and gender were extracted from the ‘patient files’ in the CPRD. Age at the index date was calculated by subtracting the year of the index date from the year of birth. Socioeconomic status was derived from the CPRD Index of Multiple Deprivation 2015 database. Patients with missing individual-level IMD scores were given their practices' IMD scores as a replacement. The geographical locations of the general practices were grouped into ten areas: North East, North West, Yorkshire & the Humber, East Midlands, East of England, South West, South Central, London and South East Coast. The number of patients registered in each area was calculated.

Baseline comorbidities

Baseline comorbidities are defined as comorbidities that may influence gabapentinoid use, including alcohol use problems, mental health disorders (anxiety and depression), diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), epilepsy, psychoactive substance misuse, in the 12 months before the index date. Patients’ baseline comorbidities were identified by applying the corresponding medical code lists (Section 5.4.1) in CPRD GOLD clinical files and Aurum observation files.

Baseline general health condition is defined as the optimised Charlson Comorbidity Index (CCI) (Section 5.4.1) measured in the 12 months before the index date. The higher the CCI score, the worse the patient’s health condition; patients who score 0 for CCI have no serious disease. Comorbidities included in the optimised CCI list

were identified from the CPRD for the study cohort and weighted to generate the baseline CCI score for individual patients.

A sensitivity analysis looking back for 36 months before the index date was conducted to capture the comorbidity records in patients who did not visit the GP or did not get the repeated diagnosis recorded by GP annually. If a patient did not have 36 months of observation before the index date, any time available before the index date was included in the sensitivity analysis.

Baseline pain medication use

Baseline pain medication use is defined as the prescription of medicines that are relevant to the prescribing of gabapentinoids (opioids, benzodiazepines, antidepressants, and Z-drugs) in the 12 months before the index date. The exposure to pain-related medicines in the 12 months after the index date was also measured to compare the use of pain-related medicines before and after gabapentinoid initiation. Patients' baseline pain medication use was identified using product code lists (Section 5.4.2) from the CPRD therapy files or drug issue files.

Opioid prescriptions were further categorised into strong opioids and weak opioids according to their potency of pain-relieving [224]. Antidepressants were categorised by the WHO Anatomical Therapeutic Chemical (ATC) classification system [225] into tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). Benzodiazepines were categorised by their indications into benzodiazepines for hypnotics and anxiolytics [8]. The percentage of patients that were prescribed each category of drugs in either the 12 months before or the 12 months after the index date was calculated for both cohorts (Equation 6-1).

$$Percentage = \frac{Number\ of\ patients\ being\ prescribed\ the\ drug}{Number\ of\ patients\ in\ the\ cohort} \times 100\%$$

Equation 6-1. The calculation used for the percentage of drug use in a population

In the gabapentinoid user cohort, the *time to initiation* of gabapentinoids is defined as the time from the study entry date (i.e. diagnosis with CNCP) to the index date.

6.3.4. Analytical methods

Descriptive statistics were used to report baseline demographics, comorbidities and pain medication use. Clinical records for the study cohorts were identified from CPRD GOLD and CPRD Aurum separately and combined into a single CPRD dataset for all of the analyses. Mean and standard deviation (SD) were used to report age and time to initiation; median and the interquartile range (IQR) were used for reporting the IMD decile. Number and percentage were used to report gender, baseline comorbidities and pain medication use in both cohorts. Differences in baseline characteristics between gabapentinoid users and non-users were tested by t-tests and Pearson chi-square tests at a 95% significance level according to the type of the variables (i.e. continuous or categorical).

Logistic regression (Appendix 5) was applied to evaluate the association between the gabapentinoid initiation in patients with CNCP (dependent variable) and the influential baseline characteristics (independent variables). Subgroup analyses were conducted in gabapentin initiators and pregabalin initiators. The crude odds ratio (OR) generated in univariable analysis and the adjusted odds ratio (aOR) generated in multivariable analysis were reported with a 95% confidence interval (95% CI). The aORs of individual models were also presented as forest plots.

The influential baseline characteristics forced into the logistic regression were baseline demographics, baseline comorbidities and baseline pain medications use as described above. Backward elimination was adapted for covariate selection [226]. The diagnostic correlation table of the baseline comorbidities suggested all correlations below 0.5, so the baseline comorbidities in this study were assumed to be independent or at least not highly correlated to each other and thus no interaction term was included.

All the statistical analyses were conducted in STATA v14 (Stata-Corp, Texas, USA, 2015).

6.4. Results

6.4.1. Cohort selection

Among the CNCP population, 655,141 (7.9%) gabapentinoid users were identified and matched to 2,676,333 gabapentinoid non-users (Figure 6-2). Of the gabapentinoid users with CNCP, 464,746 (70.9%) were initiated with gabapentin and 189,958 (29.0%) were initiated with pregabalin, while 437 patients (0.1%) were initiated with both gabapentin and pregabalin on the index date.

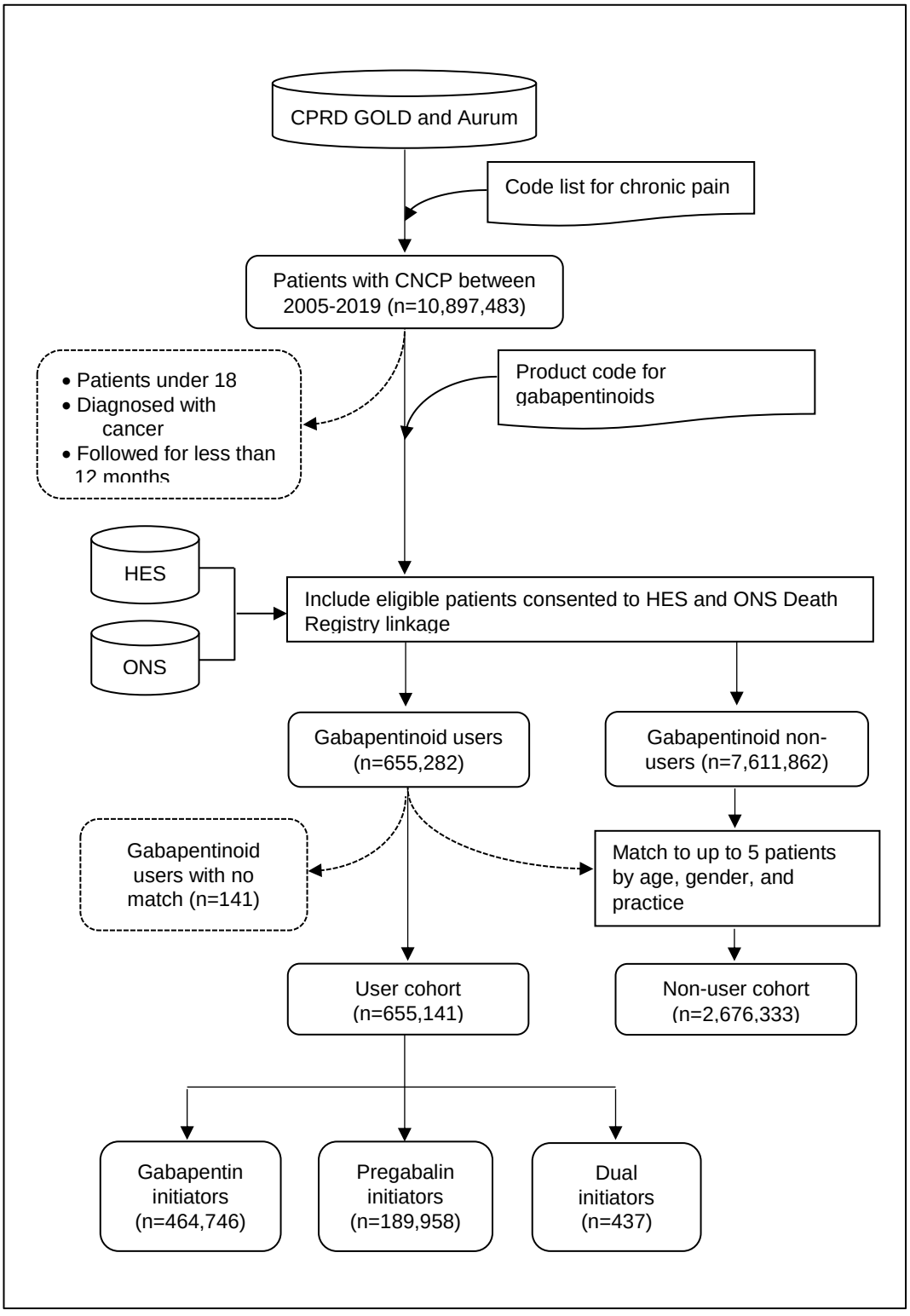


Figure 6-2. Flow chart for generating the study cohorts and sub-cohorts

6.4.2. Baseline demographics and time to gabapentinoid initiation

The mean age of gabapentinoid users at the index date was 55.91 years (SD: 16.23). Only a small proportion of gabapentinoid users with CNCP are under 40 years of age when first prescribed gabapentinoids (n=109,934, 16.8%). More female than male gabapentinoid users (n=411,066; 62.7%) were identified from the CNCP population. The socioeconomic status distribution of gabapentinoid users was more deprived than the UK average, with a median IMD decile of 6 (IQR: 3, 8) (an IMD decile of one means the least deprived). The mean time to initiation of gabapentinoids from the study entry date was 4.36 (SD: 3.88) years for gabapentinoid users. The North West of England contained the highest proportion of gabapentinoid users (n=146,506, 22.4%), followed by the West Midlands (n=111,271, 17.0%) and the South West (n=74,798, 11.4%). The East Midlands contained the lowest proportion of gabapentinoid users with CNCP (n=16,221, 2.5%). The baseline demographics of the gabapentinoid non-user cohort were similar to the gabapentinoid user cohort due to the matching process (Table 6-1).

Table 6-1. Demographics of the study cohorts

		GPN user	GPN non-user
Number of patients	Number	655,141	2,676,333
Age at index date	Mean (SD)	55.91 (16.23)	54.32 (16.02)
Age stratification (n, %)	18-40	109,934 (16.8%)	508,435 (19.0%)
	40-50	131,739 (20.1%)	572,476 (21.4%)
	51-60	143,882 (22.0%)	603,034 (22.5%)
	61-70	120,400 (18.4%)	471,563 (17.6%)
	71-80	95,082 (14.5%)	342,332 (12.8%)
	81-90	47,179 (7.2%)	157,321 (5.9%)
	91-100	6,849 (1.0%)	21,039 (0.8%)
	>100	76 (0.0%)	133 (0.0%)
Gender	Female (%)	411,066 (62.7%)	1,688,152 (63.1%)
IMD index	Median (IQR)	6 (3,8)	6 (3,8)
Geographical distribution (n, %)	North East	35,686 (5.4%)	143,999 (5.4%)
	North West	146,506 (22.4%)	596,954 (22.3%)
	Yorkshire & The Humber	27,467 (4.2%)	108,764 (4.1%)
	East Midlands	16,221 (2.5%)	65,337 (2.4%)
	West Midlands	111,271 (17.0%)	459,536 (17.2%)
	East of England	33,647 (5.1%)	133,080 (5.0%)
	South West	74,798 (11.4%)	299,966 (11.2%)
	South Central	67,200 (10.3%)	272,737 (10.2%)
	London	84,765 (12.9%)	362,255 (13.5%)
	South East Coast	57,565 (8.8%)	233,636 (8.7%)
Time to initiation	Mean (SD)	4.36 (3.88)	-

Note: IMD: Index of Multiple Deprivation; GPN: Gabapentinoids

6.4.3. Baseline comorbidities

The baseline comorbidities most commonly diagnosed in gabapentinoid users were mental health disorders (n=108,273, 16.5%), which include depression (n=81,388, 12.4%) and anxiety (n=52,707, 8.7%), and the next most common diagnosis was diabetes (n=66,523, 10.2%). In the 12 months before the index date, 0.6% of users had alcohol use problems (such as alcohol abuse and addiction), making them the least common comorbidities among those studied. The prevalence of all baseline

comorbidities in gabapentinoid non-users was significantly lower than users (Table 6-2 (a)).

The percentage of patients that had a baseline CCI score of 0 was much lower in gabapentinoid users than non-users (72.2% of gabapentinoid users vs. 82.9% of gabapentinoid non-users). A greater proportion of Gabapentinoid users than non-users were represented for all CCI scores over 0 (Table 6-2 (a)).

The sensitivity analyses looking back for 36 months identified more comorbidities and generated higher CCI scores, but this did not change the difference between gabapentinoid users and non-users or the most and least common comorbidities in the cohorts (Table 6-2 (b)).

Table 6-2. Baseline comorbidities in gabapentinoid users and non-users in the 12 months and 36 months before the index date

	GPN user	GPN non-user	P value
(a) 12 months before the index date			
Baseline comorbidities			
Mental health disorder	108,273 (16.5%)	223,060 (8.3%)	<0.001
Depression	81,388 (12.4%)	157,881 (5.9%)	<0.001
Anxiety	52,707 (8.0%)	109,292 (4.1%)	<0.001
Diabetes	66,523 (10.2%)	159,876 (6.0%)	<0.001
CKD	14,849 (2.3%)	38,876 (1.5%)	<0.001
COPD	21,964 (3.4%)	49,716 (1.9%)	<0.001
Epilepsy	8,080 (1.2%)	16,657 (0.6%)	<0.001
Psychoactive substance misuse	4,691 (0.7%)	5,410 (0.2%)	<0.001
Alcohol use problem	3,716 (0.6%)	6,889 (0.3%)	<0.001
Baseline Charlson Comorbidity Index			<0.001
0	473,087 (72.2%)	2,218,519 (82.9%)	
1	128,729 (19.6%)	352,620 (13.2%)	
2	28,777 (4.4%)	61,987 (2.3%)	
3	17,387 (2.7%)	33,558 (1.3%)	
4	4,730 (0.7%)	6,630 (0.2%)	
5	1,525 (0.2%)	2,083 (0.1%)	
6	683 (0.1%)	719 (0.0%)	
7	152 (0.0%)	161 (0.0%)	
≥8	71 (0.0%)	56 (0.0%)	
(b) 36 months before the index date			
Baseline comorbidities			
Mental health disorder	192,467 (29.4%)	444,628 (16.6%)	<0.001
Depression	148,987 (22.7%)	316,001 (11.8%)	<0.001
Anxiety	99,474 (15.2%)	233,937 (8.7%)	<0.001
Diabetes	83,573 (12.8%)	200,835 (7.5%)	<0.001
CKD	30,634 (4.7%)	83,131 (3.1%)	<0.001
COPD	31,221 (4.8%)	70,746 (2.6%)	<0.001
Epilepsy	11,385 (1.7%)	24,894 (0.9%)	<0.001
Psychoactive substance misuse	8,303 (1.3%)	10,297 (0.4%)	<0.001
Alcohol use problem	7,803 (1.2%)	15,128 (0.6%)	<0.001
Charlson Comorbidity Index			<0.001
0	416,922 (63.6%)	2,040,325 (76.2%)	
1	149,581 (22.8%)	439,162 (16.4%)	
2	41,373 (6.3%)	99,843 (3.7%)	
3	29,201 (4.5%)	67,548 (2.5%)	
4	10,808 (1.6%)	18,373 (0.7%)	
5	4,319 (0.7%)	7,230 (0.3%)	
6	2,013 (0.3%)	2,783 (0.1%)	
7	664 (0.1%)	816 (0.0%)	
≥8	260 (0.0%)	253 (0.0%)	

Note: CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease

6.4.4. Pain medication use before and after the index date

A significantly higher percentage of gabapentinoid users were prescribed pain medications (higher in all categories and sub-categories of pain medications) in the 12 months before the index date than non-users (Table 6-3). Opioids (56.5%), especially weak opioids (44.8%), had been prescribed to over half of the gabapentinoid users before the index date, with a considerable number of gabapentinoid users being prescribed both strong and weak opioids (13.8%). Similarly, gabapentinoid users were commonly prescribed antidepressants (46.7%) in the 12 months before the index date, especially TCAs (30.9%). Some gabapentinoid users were prescribed benzodiazepines (13.6%) or Z-drugs (6.2%) before the index date.

The percentage of gabapentinoid users that were prescribed pain medications in the 12 months after the index date was slightly higher than the percentage in the 12 months before (Table 6-3). For gabapentinoid non-users, the change in prescriptions before and after the dummy index date was lower than 1.5% for all pain medication categories and sub-categories. This is unsurprising, as the dummy index date has no particular significance for the gabapentinoid non-user cohort. In contrast, for gabapentinoid users, the prescribing of some pain medications noticeably changed before and after the index date. For example, the percentage of gabapentinoid users that were prescribed strong opioids increased by 5.5 percentage points after the index date. Similarly, SSRIs and SNRIs prescribed to gabapentinoid users increased by 4.3 and 2.7 percentage points respectively. TCAs and weak opioids prescribed to gabapentinoid users after the index date decreased by 4.2 and 2.0 percentage points respectively.

Table 6-3. Pain medication use before and after the index date

	12 months *before* the index date			12 months *after* the index date		
	GPN user	**GPN non-user**	**P values**	**GPN user**	**GPN non-user**	**P values**
Opioids						
All	369,846 (56.5%)	573,490 (21.4%)	<0.001	393,004 (60.0%)	536,992 (20.1%)	<0.001
Strong opioids	167,231 (25.5%)	131,178 (4.9%)	<0.001	203,076 (31.0%)	132,641 (5.0%)	<0.001
Weak opioids	293,679 (44.8%)	498,772 (18.6%)	<0.001	280,319 (42.8%)	460,182 (17.2%)	<0.001
Antidepressants						
All	305,935 (46.7%)	485,331 (18.1%)	<0.001	321,730 (49.1%)	496,179 (18.5%)	<0.001
TCAs	202,310 (30.9%)	180,118 (6.7%)	<0.001	175,165 (26.7%)	180,045 (6.7%)	<0.001
MAOIs	267 (0.0%)	292 (0.0%)	<0.001	295 (0.0%)	280 (0.0%)	<0.001
SSRIs	120,145 (18.3%)	289,681 (10.8%)	<0.001	147,960 (22.6%)	297,381 (11.1%)	<0.001
SNRIs	24,902 (3.8%)	29,997 (1.1%)	<0.001	42,863 (6.5%)	31,759 (1.2%)	<0.001
Benzodiazepines						
All	89,225 (13.6%)	113,871 (4.3%)	<0.001	90,408 (13.8%)	107,154 (4.0%)	<0.001
Hypnotics	14,790 (2.3%)	22,999 (0.9%)	<0.001	16,824 (2.6%)	21,231 (0.8%)	<0.001
Anxiolytics	77,879 (11.9%)	93,296 (3.5%)	<0.001	77,361 (11.8%)	88,050 (3.3%)	<0.001
Z drugs						
All	40,830 (6.2%)	67,161 (2.5%)	<0.001	51,138 (7.8%)	67,078 (2.5%)	<0.001

Note: GPN: Gabapentinoids; TCA: Tricyclic antidepressant; MAOI: MonoAmine Oxidase Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Noradrenaline Reuptake Inhibitor

6.4.5. Baseline characteristics associated with gabapentinoid initiation

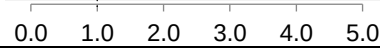
All baseline comorbidities and pain medication uses are significantly associated with gabapentinoid initiation (Table 6-4a). The strongest influential factor among the studied baseline characteristics for gabapentinoid initiation is baseline TCA use (aOR: 4.18, 95% CI: 4.14, 4.21), followed by baseline strong opioid use (aOR: 4.08, 95% CI: 4.05, 4.12). Among the studied baseline comorbidities, baseline substance misuse (aOR: 1.91, 95% CI: 1.82, 1.99) and epilepsy (aOR: 1.91, 95% CI: 1.85, 1.97) are the strongest comorbidities that indicate gabapentinoid initiation.

Subgroup analyses of gabapentin and pregabalin show results similar to the primary analysis (Table 6-4 b), but several differences were found in the logistic regression results between gabapentin and pregabalin. The baseline use of MAOIs, hypnotics, and Z-drugs which are significantly associated with gabapentinoid initiation, does not have a significant association with gabapentin initiation. However, the strongest influential factor for gabapentin initiation is the same as for gabapentinoids; the baseline use of TCA (aOR: 3.47, 95% CI: 3.45, 3.50), followed by baseline strong opioid use (aOR: 3.06, 95% CI: 3.03, 3.08). All studied baseline characteristics are associated with pregabalin initiation, but the strongest influential factor for pregabalin initiation is baseline use of MAOIs (aOR: 3.41, 95% CI: 2.78, 4.18) rather than TCAs.

Table 6-4. Association between baseline characteristics and gabapentinoid initiation in patients with CNCP

(a) Primary analysis for gabapentinoids

	OR **(95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Baseline comorbidities			
Alcohol use problem	2.24 (2.15, 2.33)*	1.28 (1.22, 1.34)*	
Depression	2.30 (2.28, 2.32)*	1.46 (1.44, 1.47)*	
Anxiety	2.08 (2.06, 2.10)*	1.29 (1.27, 1.30)*	
Diabetes	1.80 (1.78, 1.82)*	1.45 (1.43, 1.46)*	
CKD	1.58 (1.55, 1.61)*	1.19 (1.16, 1.22)*	
COPD	1.86 (1.83, 1.89)*	1.22 (1.19, 1.24)*	
Epilepsy	2.01 (1.95, 2.06)*	1.91 (1.85, 1.97)*	
Substance misuse	3.64 (3.50, 3.79)*	1.91 (1.82, 1.99)*	
Baseline pain medication use			
Opioids			
Strong opioids	7.00 (6.95, 7.06)*	4.08 (4.05, 4.12)*	
Weak opioids	3.63 (3.61, 3.66)*	2.40 (2.38, 2.41)*	
Antidepressants			
TCA	6.46 (6.41, 6.51)*	4.18 (4.14, 4.21)*	
MAOI	3.81 (3.22, 4.51)*	2.57 (2.13, 3.09)*	
SSRI	1.88 (1.87, 1.89)*	1.13 (1.12, 1.14)*	
SNRI	3.61 (3.55, 3.68)*	1.96 (1.92, 2.00)*	
Benzodiazepines			
Hypnotics	2.72 (2.66, 2.78)*	1.10 (1.08, 1.13)*	
Anxiolytics	3.83 (3.80, 3.87)*	1.87 (1.85, 1.90)*	
Z-drugs			
All	2.64 (2.61, 2.68)*	1.21 (1.19, 1.23)*	
Baseline demographics			
Gender	0.99 (0.99, 1.00)*	0.82 (0.82, 0.83)*	
Age	1.01 (1.01, 1.01)*	1.00 (1.00, 1.00)*	
IMD	1.03 (1.03, 1.03)*	1.00 (1.00, 1.00)*	



*Note: (1) CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; TCA: Tricyclic Antidepressants; MAOI: Monoamine-Oxidase Inhibitors; SSRI: Selective Serotonin Re-uptake inhibitors; SNRI: Serotonin-Noradrenaline Reuptake Inhibitors; IMD: Index of Multiple Deprivation; (2) * suggests statistically significant results*

(b) Subgroup analysis for gabapentin and pregabalin

	Gabapentin		Pregabalin	
	OR (95% CI)	**aOR (95% CI)**	**OR (95% CI)**	**aOR (95% CI)**
Baseline comorbidities				
Alcohol use problem	1.86 (1.78, 1.95)*	1.23 (1.17, 1.29)*	2.29 (2.16, 2.42)*	1.18 (1.10, 1.25)*
Depression	1.81 (1.79, 1.83)*	1.24 (1.23, 1.26)*	2.61 (2.57, 2.64)*	1.48 (1.46, 1.51)*
Anxiety	1.49 (1.47, 1.51)*	0.98 (0.97, 1.00)*	2.82 (2.78, 2.87)*	1.70 (1.67, 1.73)*
Diabetes	1.71 (1.70, 1.73)*	1.33 (1.32, 1.35)*	1.61 (1.58, 1.63)*	1.37 (1.34, 1.39)*
CKD	1.54 (1.51, 1.58)*	1.14 (1.11, 1.16)*	1.42 (1.37, 1.47)*	1.18 (1.14, 1.22)*
COPD	1.83 (1.80, 1.86)*	1.22 (1.19, 1.24)*	1.51 (1.47, 1.55)*	1.07 (1.04, 1.10)*
Epilepsy	1.50 (1.46, 1.55)*	1.36 (1.31, 1.41)*	2.54 (2.44, 2.63)*	2.28 (2.19, 2.37)*
Substance misuse	2.14 (2.04, 2.24)*	1.20 (1.14, 1.26)*	4.46 (4.25, 4.68)*	2.27 (2.16, 2.40)*
Baseline pain medication use				
Opioids				
Strong opioids	5.31 (5.26, 5.35)*	3.06 (3.03, 3.08)*	4.05 (4.01, 4.10)*	2.42 (2.39, 2.45)*
Weak opioids	3.50 (3.48, 3.52)*	2.35 (2.34, 2.37)*	2.41 (2.38, 2.43)*	1.59 (1.58, 1.61)*
Antidepressants				
TCA	5.38 (5.34, 5.43)*	3.47 (3.45, 3.50)*	3.52 (3.48, 3.56)*	2.22 (2.19, 2.25)*
MAOI	1.76 (1.44, 2.15)*	-	5.81 (4.80, 7.03)*	3.41 (2.78, 4.18)*
SSRI	1.68 (1.67, 1.70)*	1.15 (1.14, 1.16)*	1.89 (1.87, 1.91)*	1.07 (1.06, 1.09)*
SNRI	2.21 (2.17, 2.26)*	1.23 (1.20, 1.26)*	4.33 (4.24, 4.43)*	2.25 (2.20, 2.30)*
Benzodiazepines				
Hypnotics	2.23 (2.18, 2.28)*	-	2.56 (2.49, 2.64)*	1.16 (1.12, 1.20)*
Anxiolytics	2.88 (2.85, 2.91)*	1.47 (1.45, 1.49)*	3.45 (3.40, 3.49)*	1.70 (1.68, 1.73)*
Z-drugs				
All	1.99 (1.96, 2.02)*	-	2.93 (2.88, 2.98)*	1.42 (1.39, 1.44)*
Baseline demographics				
Gender	0.98 (0.98, 0.99)*	0.84 (0.83, 0.84)*	1.01 (1.01, 1.02)*	0.88 (0.88, 0.89)*
Age	1.01 (1.01, 1.01)*	1.00 (1.00, 1.00)*	1.00 (1.00, 1.00)*	1.00 (1.00, 1.00)*
IMD	1.03 (1.03, 1.03)*	1.00 (1.00, 1.01)*	1.02 (1.02, 1.02)*	0.99 (0.99, 0.99)*

*Note: (1) CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; TCA: Tricyclic Antidepressants; MAOI: Monoamine-Oxidase Inhibitors; SSRI: Selective Serotonin Re-uptake inhibitors; SNRI: Serotonin-Noradrenaline Re-uptake Inhibitors; IMD: Index of Multiple Deprivation; (2) * suggests statistically significant results*

6.5. Discussion

Gabapentinoid users with CNCP in English primary care have a mean age of 55.91 years at the index date, are more likely to be female (62.7%), and tend to have a poorer socioeconomic status than non-users. A significantly higher percentage of gabapentinoid users than non-users had baseline comorbidities and pain medication use. Around half of gabapentinoid users were prescribed opioids in the year before gabapentinoid initiation, and a similar amount were prescribed antidepressants. Patients' baseline comorbidities and baseline pain medication use are significantly associated with gabapentinoid initiation. Of these, baseline TCA use, baseline strong opioid use, baseline psychoactive substance misuse, and baseline diagnosis of epilepsy are all strongly associated with gabapentinoid initiation in patients with CNCP.

The subgroup analyses suggest that baseline use of MAOIs, hypnotics, and Z-drugs are not associated with gabapentin initiation, but are significantly associated with pregabalin initiation. This could be due to the slightly different indications between gabapentin and pregabalin, as pregabalin is additionally indicated for generalised anxiety disorder [8]. The use of MAOIs, hypnotics, and Z-drugs could be associated with the initiation of pregabalin for anxiety, which is supported by the aOR for anxiety (gabapentin aOR: 0.98, 95% CI: 0.97, 1.00 vs. pregabalin aOR 1.70, 95% CI: 1.67, 1.73).

Previous studies found similar baseline characteristics in gabapentinoid users, although none of them were conducted in the CNCP population. Torrance *et al.* (2020) identified 29,111 gabapentinoid users from two NHS Health Board regions in Scotland, and found that patients who had three or more prescriptions of gabapentinoids in 2016 had a mean age of 58.1 years, were mostly female (52.5%), were more likely to live in deprived areas, and had a high proportion of co-

prescribed opioids and benzodiazepines [88]. Pauly *et al.* (2020) identified gabapentin users from a US commercial insurance database during 2009-2016 and found gabapentin users were more likely to be female and aged 55-64 years [227]. Appleyard *et al.* (2019) found the incidence rate of first gabapentinoid prescriptions among new osteoarthritis patients in the UK increased more in females from 2005 [87].

This is the first study to match and compare gabapentinoid users with non-users in the CNCP population. A similar comparison between gabapentin users and non-users had been conducted in the US. Pauly *et al.* (2020) conducted a cross-sectional comparison of gabapentin users (n=536,488) and non-users (n=19,266,873) in the US IBM Marketscan Commercial Claims and Encounters Database in 2016 [227]. The result showed a significant difference between gabapentin users and non-users for opioid use (60.8% of gabapentin users vs. 16.5% of gabapentin non-users), seizure disorders (25.9 vs. 6.3 per 1000 patients), neuropathic pain (506.6 vs 80.1 per 1000 patients), mental health disorders (506.6 vs 80.1 per 1000 patients), substance use disorders (162.8 vs 37.3 per 1000 patients), and diabetes (303.9 vs 101.3 per 1000 patients) [227]. However, their study included all the patients registered with the database, and therefore the age and gender distribution of the gabapentin users and non-users were significantly different, which caused a large difference in the baseline characteristics between the two cohorts. In contrast, this study matches patients by age, gender, and practice, which minimises the influence of baseline demographics and provides a better comparison of baseline characteristics.

The finding that patient-level baseline characteristics are associated with gabapentinoid initiation in this study supports and helps explain the result in Chapter 3 that practice-level disease prevalence is significantly associated with

gabapentinoid prescribing in general practices. Although no previous study had investigated the factors associated with gabapentinoid initiation, one study showed a supportive result. *Johansen* identified gabapentinoid users from the US Medical Expenditure Panel Survey data during 2002-2015 and measured the characteristics of gabapentinoid users in a cross-sectional study. It found that the proportion of gabapentinoid users with diabetes, many comorbidities (≥ 5), and opioid or benzodiazepine prescriptions significantly increased over time [92].

Some of the baseline characteristics found associated with gabapentinoid initiation in this study are factors that have been found to be associated with gabapentinoid harm. A cohort study identified anticonvulsant users between July 2001 and December 2006 in the HealthCore Integrated Research Database in the US, and found gabapentin users with mood disorders and with epilepsy had an increased risk of suicide [111]. A literature review focusing on the misuse and abuse of gabapentinoids suggested that physicians should be careful with prescribing gabapentinoids to patients who have a drug abuse history in order to reduce harm [112]. Two studies found that co-prescription of gabapentinoids with opioids increased the risk of opioid-related death in Canada [22, 23]. A post-mortem study of deaths involving gabapentin and pregabalin in London and South East England from 2016 to 2017 found the most common drugs identified with gabapentinoids were non-heroin-related opioids (gabapentin: 60.2%, pregabalin: 64.6%) [107].

Gabapentinoid users were found to have more baseline risk factors related to gabapentinoid-related harms (such as suicide, drug misuse and abuse, and drug-related death) than gabapentinoid non-users. Therefore, it is important to investigate the risk of serious adverse events in gabapentinoid users in future studies, and consider the confounding effect of the baseline characteristics that were found to be associated with gabapentinoid initiation in this study.

This study used patient-level data from a representative primary care database in England, which includes rich GP consultation and prescribing information to enable a comprehensive understanding of the patient's baseline characteristics. The baseline characteristics were identified using rigorously developed code lists from the database. Gabapentinoid users with CNCP were matched to non-users to provide a comparison of the baseline characteristics. The baseline pain medication use before and after the index date was compared to understand the change in pain medication needs before and after gabapentinoid initiation. The association between the baseline characteristics and the gabapentinoid initiation was investigated using logistic regression, and the association was tested in the subgroup analyses to differentiate between gabapentin and pregabalin.

However, there are still some limitations in this study. Firstly, the disease code lists in this study were not developed from scratch but instead were referenced from published research, so may not fit perfectly with the study question. For example, the diabetes code list used in this study includes any type 1 or type 2 diabetes, but it may have been more appropriate to use diabetes with complications for this study, as neuropathic pain is a common symptom among patients with diabetes that have foot complications. Secondly, EHR databases can only provide information as recorded in the GP system, which may not reflect actual medication use or disease conditions of patients. For example, in this study chronic pain was identified using diagnoses that are very likely to develop long-term pain. However, a pain diagnosis indicating long-term pain cannot guarantee the pain did last for a long time. Thirdly, some influential factors were not adjusted for in the regression analysis because missing data and unavailable information are common in secondary databases. For example, the level of pain and the pain category (by mechanism or symptom) are often not recorded because they are not tested in every patient. Similarly, an

accurate body mass index was not available as a quarter of the CPRD-registered patients had missing weight or height information [38]. Among the 77% of the CPRD registrants that had weight and height data between 2005 and 2011, a third of them had outdated body mass index relevant data (recorded over 3 years ago) [38].

This chapter provides an overview of the baseline characteristics of gabapentinoid users and suggests a significant difference between gabapentinoid users and matched non-users. It identifies a set of baseline factors that are associated with gabapentinoid initiation, some of which are risk factors for gabapentinoid-related harms. Since gabapentinoid users with CNCP are more likely to have poor health conditions and polypharmacy than gabapentinoid non-users, their risk of experiencing gabapentinoid-related harm is elevated. Therefore, it is worth exploring the risk of serious adverse events in gabapentinoid users in future studies.

Chapter 7. The risk of serious adverse events in gabapentinoid users and non-users with chronic non-cancer pain in English primary care

7.1. Introduction

The rapid increase in gabapentinoid prescribing in English primary care from 2013 (Chapter 3) raised concerns about gabapentinoid safety in the sizeable gabapentinoid user population. The common side effects of gabapentinoids reported in the British National Formulary (BNF) include dizziness, drowsiness, diarrhoea, and many others [8]. Warnings on gabapentinoids on the risk of severe respiratory inhibition, suicidal thoughts and behaviour, and abuse and dependence were sounded in recent years [8]. A study of gabapentinoid-related adverse reactions using records from the French Pharmacovigilance System found that the most frequently occurring adverse reactions from 1995 to 2009 were neuropsychiatric reactions, including drowsiness, confusion, and dizziness [228].

In addition to the well-known side effects, exploration of the rare or 'hard-to-notice' side effects of gabapentinoids has also advanced over time. A Dutch case report presented hypoglycaemia in six patients (both with and without diabetes) after exposure to gabapentin between 2002 and 2012 [229]. In the US and Japanese spontaneous reporting systems for adverse drug events, the reported odds ratio of adverse events related to falls (i.e. somnolence, dizziness, loss of consciousness, and falls) is higher for pregabalin than for other drugs. Most fall-related adverse events relevant to pregabalin were reported shortly after the initiation of pregabalin, with a median onset of two days [230]. Moreover, deaths involving gabapentinoids in England increased rapidly between 2004 and 2020, as identified by the National Programme on Substance Abuse Deaths (NPSAD) [108]. Given the sizeable

gabapentinoid user population, gabapentinoid-related adverse events could incur a considerable healthcare burden. A US study from 2013-2015 found patients who overused gabapentin had greater utilisation of health services such as inpatient hospitalisation and emergency care [231].

However, there is still a lack of robust epidemiological evidence of severe gabapentinoid-related adverse events (ADEs). None of the above literature directly compared the incidence rates of serious adverse events between gabapentinoid users and non-users. Notably, there are noticeable differences in the baseline characteristics between gabapentinoid users and non-users in the CNCP population (Chapter 6). The poorer baseline health conditions and higher rates of baseline pain medication use in gabapentinoid users may result in a higher incidence of ADEs.

To investigate the hypothesis that gabapentinoid use is associated with a higher risk of serious adverse events, this chapter compares the incidence of serious adverse events in gabapentinoid users with non-users in patients with CNCP. It investigates the association between gabapentinoids and serious adverse events, accounting for the different baseline characteristics between users and non-users.

7.2. Aim and objectives

This chapter is a hypothesis-testing study that compares the risk of serious adverse events in gabapentinoid users and non-users with CNCP. The objectives are:

(1) To generate the crude incidence rate and incidence rate ratio of serious adverse events in gabapentinoid users and non-users with CNCP;
(2) To compare the survival curves of serious adverse events in gabapentinoid users and non-users with CNCP;

(3) To investigate the association between gabapentinoid exposure and the risk of following serious adverse events in patients with CNCP, while adjusting for confounding factors.

7.3. Methods

7.3.1. Study design and data sources

This retrospective matched cohort study used primary care data from the CPRD and linked to external databases, including the Office for National Statistics (ONS) Death Registry and Hospital Episode Statistics (HES) Admitted Patient Care (APC) databases (Section 5.3, Chapter 5). The databases were linked to provide a complete follow-up of the serious adverse events, as they are more likely to be treated in a hospital than in primary care.

A cohort study is an appropriate method to investigate the risk of serious adverse events in gabapentinoid users and non-users with CNCP because they can examine multiple outcomes simultaneously in one set of cohorts [232]. In this study, study cohorts of gabapentinoid users and non-users with CNCP were followed from the index date to the study exit date to look for the first incidence of each serious adverse event. This can be seen as several cohort studies conducted simultaneously on the same cohorts, with each focused on a different outcome (a different serious adverse event).

7.3.2. Study population

The study cohorts are defined as *gabapentinoid users* and matched *gabapentinoid non-users* from the patients with CNCP identified between January 2005 and

December 2019. The identification and matching process is described in Chapter 6 (Section 6.3.2).

The study entry date (a patient's first eligible diagnosis of CNCP during the observation period) and study exit date are defined in Chapter 5 (Section 5.5.1). The index date for the gabapentinoid user cohort and the dummy index date for the gabapentinoid non-user cohort were defined in Chapter 6 (Section 6.3.2). The observation period for the serious adverse events starts on the index date (or dummy index date) and ends on the study exit date (Figure 7-1).

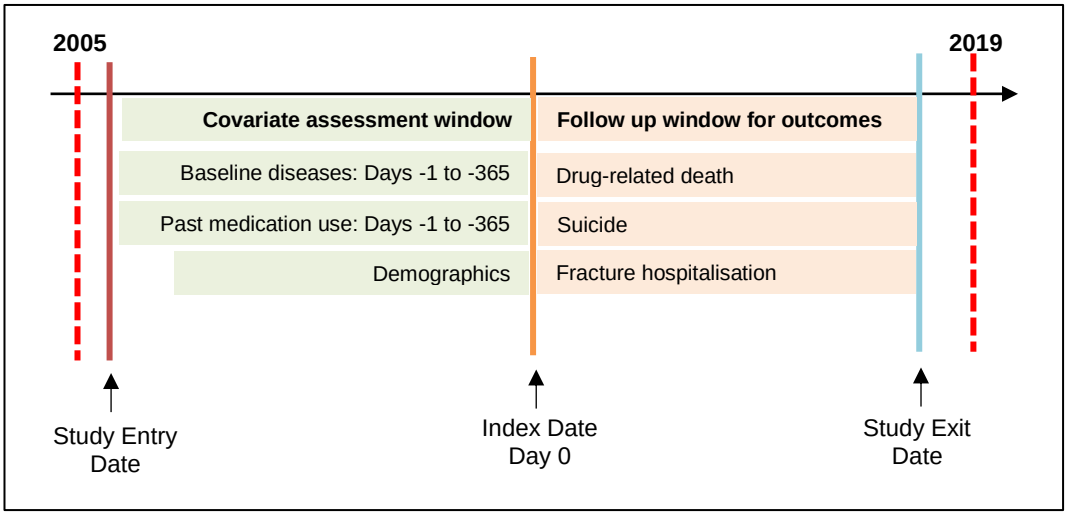


Figure 7-1. Definition of the follow-up period for the matched cohort study

7.3.3. Outcome measures

Serious adverse events

The serious adverse events in this study are defined as drug-related death, suicide death, suicide hospitalisation, and fracture hospitalisation that occur after the index date.

Despite the low incidence rate, deaths are the most serious adverse events, and cause significant societal loss. Drug-related deaths (i.e. death related to drug poisoning) and suicide deaths were selected in this study due to their plausible link with gabapentinoids' mechanisms [233, 234]. Similarly, fracture and suicide hospitalisations were targeted as serious adverse events considering their burden on patients and society, and the plausible link to gabapentinoids' mechanisms [233-236].

Cases of drug-related death and suicide-related death were identified using ICD-10 code lists (Section 5.4.3, Chapter 5) from the ONS Death Registration dataset. Deaths in the database that include the ICD-10 codes for drug-related death or suicide death (Table 5-6) in any of the causes, regardless of the main cause or other causes, were identified as cases. The data linkage process identified a mismatch in death dates between the CPRD primary care database and the ONS Death Registration dataset. In instances where the death date record in the CPRD was not the same as in the ONS Death Registration, the earliest of the dates was used for the following analysis [237].

Cases of fracture hospitalisations and suicide hospitalisations were identified using the ICD-10 code lists for fracture (Appendix 4) and suicide (Table 5-7) from the HES APC. This study intends to identify hospitalisations caused by the serious adverse events rather than incidental adverse events recorded at hospital admission. Thus, only ICD-10 codes for fracture or suicide that were recorded as the primary diagnosis of the episode were included. Events that had a second diagnosis with the same ICD-10 code in the 14 days after admission were excluded because they were assumed to be a repeat record of the previous event due to the nature of hospital episode recording. This is because a single event can be repeatedly recorded if a patient is seen by more than one consultant during a hospital stay.

The serious adverse events were identified between the index date and the study exit date in the two cohorts. Unlike drug-related death and suicide death, which can only occur once in a patient's life, hospitalisations can happen more than once during the follow-up period. Since this study aims to understand the occurrence of the serious adverse event after the first gabapentinoid exposure rather than the number of serious adverse events, only the first fracture and suicide hospitalisations were included in the analysis. Time-to-event (TTE) is defined as the time between the index date and the date of the serious adverse event.

Fracture and suicide hospitalisations could be recurrent and dependent on previous history (i.e. non-independent occurrence) [238, 239], i.e. patients with a previous fracture or suicide hospitalisation may have a higher risk of a recurrent event compared with those who do not have pre-existing history. To account for this non-independent occurrence, patients who had a fracture or suicide hospitalisation before the index date (dummy index date) were excluded from the study cohorts in the sensitivity analyses of the corresponding events.

Baseline characteristics

The baseline demographics are defined as the age, gender, and socioeconomic status (i.e. IMD decile) of the study population at the index date. The baseline comorbidities are defined as diagnoses of alcohol use problems, anxiety, depression, diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), epilepsy, and psychoactive substance misuse in the 12 months before the index date. Baseline pain medication use is defined as the prescription of opioids (strong and weak), benzodiazepines (hypnotics and anxiolytics), antidepressants (TCAs, SSRIs, SNRIs, MAOIs), and Z-drugs in the 12

months before the index date. The identification process of the baseline characteristics is described in Section 6.3.3.

These baseline characteristics were considered to be confounding factors that need adjustment in the statistical analysis to model the association between exposure and outcome accurately. The selection of the confounding factors adapted a disjunctive cause criterion approach, where pre-exposure covariates that could be the cause of the exposure, the outcome, or both, are controlled [240]. The baseline characteristics were found to be associated with the prescribing of gabapentinoids (Chapter 6) and the occurrence of the serious adverse events [20, 22, 23, 241-243], and were therefore treated as confounding factors in the model. However, since the serious adverse events defined in this study have differing mechanisms and thus differing influential factors, a statistical approach is further adapted in the data analysis to optimise the covariate selection [240].

7.3.4. Analytical methods

The baseline characteristics of the gabapentinoid user and non-user study cohorts have been reported in Chapter 6 (Section 6.4). The follow-up time from the index date to the study exit date, which was not measured in Chapter 6, was reported as mean and SD for the two study cohorts in this study. TTE for each serious adverse event was reported as mean and SD for both cohorts. The number and proportion of patients who experienced the serious adverse events in the two cohorts were reported.

Incidence rate and incidence rate ratio

For both cohorts (gabapentinoid users and non-users), the incidence rates (IRs) per 1000 patient-years for the serious adverse events were calculated by dividing the number of patients that had an incident event after the index date by the sum of follow-up years that patients were at risk in the cohort and further multiplying by 1,000 (Equation 7-1). The at-risk follow-up time is defined as the time period from the index date to either the first relevant event date or the study exit date, whichever comes first.

$$Incidence\ rate = \frac{Number\ of\ incident\ events\ during\ the\ observation\ period\ \times 1000}{Total\ patient\ years\ at\ risk\ during\ the\ observation\ period}$$

Equation 7-1. Equation for deriving the incidence rate of the serious adverse events

For each serious adverse event (i.e., drug-related death, suicide death, fracture hospitalisation, and suicide hospitalisation), the incidence rate ratio (IRR), the ratio of IRs between gabapentinoid users and non-users, was calculated (Equation 7-2). An IRR value greater than 1 means the incidence rate of the serious adverse event is higher for gabapentinoid users.

$$Incidence\ rate\ ratio = \frac{Incidence\ rate\ in\ gabapentinoid\ users}{Incidence\ rate\ in\ gabapetinoid\ non\ users}$$

Equation 7-2. Equation for deriving incidence rate ratio

The IR and IRR were reported with a Poisson 95% confidence interval (95% CI) for the serious adverse events [244].

Kaplan-Meier estimator and log-rank test

The Kaplan-Meier estimator and the log-rank test were adapted to evaluate the risk of the serious adverse events in gabapentinoid users and non-users. In cohort studies, the full survival time is usually unknown for patients who survived until the end of follow-up or who lost follow-up before the end of the observational period, which leads to the common “right censoring” bias [245]. Both the Kaplan-Meier estimator and the log-rank test account for the loss of follow-up problem (i.e. right censoring) that is not considered in simple comparisons between IRs [245]. The Kaplan-Meier estimator was applied to estimate the survival curves of the serious adverse events [246], and log-rank tests were applied to compare the Kaplan-Meier survival curves between gabapentinoid users and non-users. The null hypothesis of the log-rank tests is that there is no difference between the tested survival curves [247].

The data in this study meet the assumptions for the Kaplan-Meier estimator and the log-rank tests: (1) censoring is not related to survival prospects (i.e. non-informative censoring); (2) the survival probabilities are the same over time for each patient, and the same for patients enrolled early and late; (3) the event date is clearly defined [248].

For each serious adverse event, the Kaplan-Meier survival curve was presented for both cohorts with the 95% CI band and the number of patients at risk for several time points during the follow-up. The results of the log-rank tests were presented as P values, where the threshold probability for rejecting the null hypothesis of the log-rank test was set as P=0.05 (two-tailed).

Cox proportional hazard models

The Cox proportional hazard model and the cause-specific hazards model were applied to investigate the association between gabapentinoid exposure (independent variable) and the risk of the serious adverse events (dependent variable). The log-rank test compares the survival curves of the serious adverse events, but only accounts for one influential factor (i.e. exposure to gabapentinoids), so can be viewed as a univariate survival analysis. Since the two cohorts in this study were matched only by age, gender, and practice, the risk of the serious adverse events could be influenced by unmatched factors. Therefore, the Cox proportional hazard model and cause-specific hazards model (which account for both the censoring problem in cohort studies and the effect of confounding factors) were applied to further investigate the associations (Appendix 5) [249].

A cause-specific proportional hazard model is an extension of the Cox proportional hazard model which censors patients with competing events separately rather than leaving them in the cohort [250]. A competing event is defined as an event that prevents the observation of the event of interest [251]. Simply censoring the competing events as a right censoring would violate the survival analysis assumption of non-informative censoring and this would cause bias [250]. In this study, the observation of suicide hospitalisation can be prevented by the occurrence of suicide death (the competing event), which is likely to happen in patients that have suicidal intentions. Therefore, a cause-specific hazard model was applied for suicide hospitalisation to account for the competing risk of suicide death [252]. Although death (non-drug-related death for drug-related death outcome) is a competing risk for all the serious adverse events in this study, it is assumed to have a minimal competing effect because the reasons causing these serious adverse events are not strongly associated with death. Not considering death as the

competing event is assumed to not bias the results largely, so a Cox proportional hazard model was applied to these serious adverse events.

The confounding factors adjusted for in the Cox proportional hazard model and cause-specific proportional hazard model are the defined baseline characteristics (demographics, comorbidities, and pain medication use, as described in Section 7.3.3). The variables were tested in both univariable and multivariable models. A backward selection process was applied for covariate selection [226]. A log-log plot of the covariates against survival time was applied to test for the proportional hazard assumption [249]. The hazard ratios (HRs) and adjusted hazard ratios (aHRs) generated by the Cox proportional hazard model and the cause-specific hazard ratios (CHRs) and adjusted cause-specific hazard ratios (aCHRs) generated by the cause-specific proportional hazard model were reported with 95% CI. The aHRs and aCHRs of gabapentinoid exposure for the serious adverse events were presented as forest plots.

In order to account for potential non-independent occurrences of fracture hospitalisations and suicide hospitalisations (Section 7.3.3), a sensitivity analysis which removed patients with any history of the event before the index date was conducted (sensitivity analysis 1). Another sensitivity analysis (sensitivity analysis 2) that included only events that occurred near the gabapentinoid exposure was conducted to draw a stronger association between gabapentinoid exposures and serious adverse events. This sensitivity analysis followed each patient for only 365 days after the index date (i.e. patients are censored on day 365 after the index date if no event is observed before then).

All statistical analyses were conducted in STATA v14 (Stata-Corp, Texas, USA, 2015).

7.4. Results

7.4.1. Cohort selection

The cohort selection process and the baseline characteristics of gabapentinoid user and non-user cohorts in this study were reported in Chapter 6 (Section 6.4), where 655,141 gabapentinoid users and 2,676,333 gabapentinoid non-users were identified from the CPRD. The mean follow-up time from the index date to the study exit date was 4.22 years (SD: 3.25) for gabapentinoid users and 3.97 (SD: 3.03) years for gabapentinoid non-users.

Among the gabapentinoid users with CNCP, 3.7% (n=24,124) experienced fracture hospitalisations, 1.6% (n=10.296) experienced suicide hospitalisations, 0.2% (n=1,339) experienced suicide death, and 0.2% (n=1,007) experienced drug-related death. The percentage of patients that experienced the serious adverse events was lower for gabapentinoid non-users (Table 7-1).

For the gabapentinoid user cohort, the mean TTE is shortest for suicide hospitalisation at 2.45 years (SD: 2.45), followed by 2.84 years (SD: 2.45) for suicide death, and 2.88 years (SD: 2.56) for drug-related death. The TTE for fracture hospitalisation is the longest among the serious adverse events at 3.32 years (SD: 2.82). The TTEs of the serious adverse events are longer in gabapentinoid non-users compared to gabapentinoid users (Table 7-1).

Table 7-1. Serious adverse events identified in the study cohorts

		Gabapentinoid user	Gabapentinoid non-user
Number of patients in the cohort	N	655,141	2,676,333
Fracture hospitalisations			
Number of patients[2]	N (%)	24,124 (3.7%)	65,302 (2.4%)
TTE	Mean (SD)	3.32 (2.82)	3.39 (2.73)
Suicide hospitalisation			
Number of patients[2]	N (%)	10,296 (1.6%)	12,812 (0.5%)
TTE	Mean (SD)	2.45 (2.45)	2.87 (2.53)
Suicide death			
Number of patients[2]	N (%)	1,339 (0.2%)	1,303 (0.0%)
TTE	Mean (SD)	2.84 (2.56)	3.09 (2.56)
Drug-related death			
Number of patients[2]	N (%)	1,007 (0.2%)	586 (0.0%)
TTE	Mean (SD)	2.88 (2.56)	2.96 (2.46)

Notes: 1. TTE: time-to-event; 2. Number of patients in the cohort that experienced the serious adverse event. For patients who have more than one fracture or suicide hospitalisation, only the first fracture or suicide hospitalisation is counted for the TTE.

7.4.2. Incidence rates of serious adverse events

Among gabapentinoid users with CNCP, the IR of new serious adverse events after the index date is highest for fracture hospitalisation, at 8.92 events per 1000 patient-years (95% CI: 8.81, 9.03), followed by suicide hospitalisation (3.76 per 1000 patient-years, 95% CI: 3.69, 3.84), suicide death (0.48 per 1000 patient-years, 95%:0.46, 0.51), and drug-related death (0.36 events per 1000 patient-years, 95% CI: 0.34, 0.39). The serious adverse events have the same order of IRs for the gabapentinoid non-users (Table 7-2).

The IRs of new serious adverse events after the index date are higher for gabapentinoid users compared to gabapentinoid non-users (Table 7-2). The largest difference in IRs between gabapentinoid users and non-users was observed for drug-related death, which has an IRR of 6.59 (95% CI: 5.95, 7.31), followed by

suicide death (IRR: 3.95, 95% CI: 3.65, 4.26). Fracture hospitalisation has the lowest IRR of 1.43 (95% CI: 1.41, 1.45).

Table 7-2. Incidence rates and incidence rate ratios of new serious adverse events after the index date in patients with CNCP

	Events (n)	Follow-up time (patient-years)	IR (95%)	IRR (95%)
Fracture hospitalisation				
Gabapentinoid users	24,124	2,703,443	8.92 (8.81, 9.03)	1.43 (1.41, 1.45)
Gabapentinoid non-users	65,302	10,484,610	6.23 (6.18, 6.28)	
Suicide hospitalisation				
Gabapentinoid users	10,296	2,736,151	3.76 (3.69, 3.84)	3.11 (3.03, 3.19)
Gabapentinoid non-users	12,812	10,593,749	1.21 (1.19, 1.23)	
Suicide death				
Gabapentinoid users	1,339	2,767,578	0.48 (0.46, 0.51)	3.95 (3.65, 4.26)
Gabapentinoid non-users	1,303	10,621,508	0.12 (0.12, 0.13)	
Drug-related death				
Gabapentinoid users	1,007	2,768,599	0.36 (0.34, 0.39)	6.59 (5.95, 7.31)
Gabapentinoid non-users	586	10,622,550	0.06 (0.05, 0.06)	

Note: IR: incidence rate per 1000 patient-years; IRR: incidence rate ratio

7.4.3. Survival curves of serious adverse events

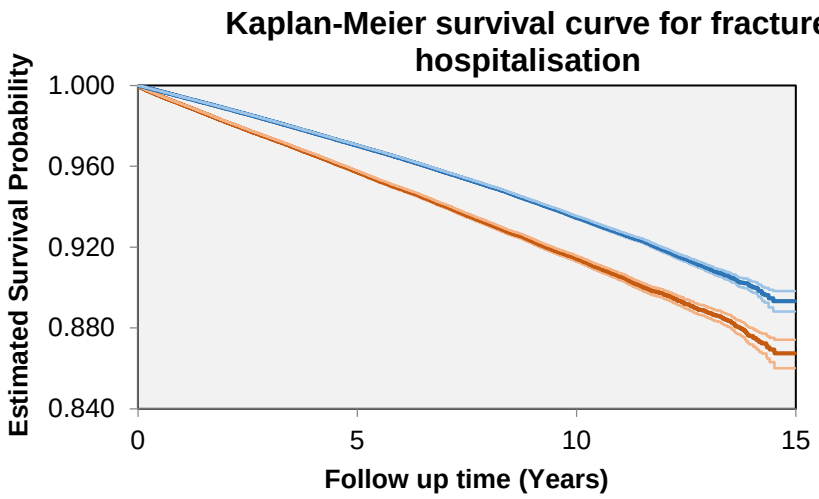
The Kaplan Meier estimated survival curves showed the estimated survival probabilities of the serious adverse events from the index date till fifteen years later (Figure 7-2). The estimated survival probabilities for the serious adverse events are high in both gabapentinoid users and non-users cohorts, with the estimated survival probabilities for both hospitalisation outcomes over 85% and for both death outcomes over 99% at year 15 of the follow-up period.

In gabapentinoid users with CNCP, the estimated survival probability of fracture hospitalisation at year 15 is 86.9%, while the estimated survival probabilities for suicide hospitalisation and suicide death are 96.2% and 99.5% respectively. The estimated survival probability of drug-related death at year 15 is 99.6%.

In gabapentinoid non-users with CNCP, the estimated survival probabilities of the serious adverse events are all higher than that in gabapentinoid users (Figure 7-2). The estimated survival probabilities of fracture hospitalisation, suicide hospitalisation, suicide death and drug-related death are 89.6%, 98.4%, 99.8% and 99.9%, respectively.

By year 15, gabapentinoid users are 4.83 times more likely to die due to drug poisoning than non-users. Gabapentinoid users are also 2.37 times more likely to experience suicide death, 1.33 times more likely to experience suicide hospitalisation, and 1.26 times more likely to experience fracture hospitalisation by year 15.

The P values of log-rank tests for drug-related death, suicide death, suicide hospitalisation, and fracture hospitalisation were all lower than 0.001 (Figure 7-2), indicating gabapentinoid use is a significant influential factor for the occurrence of the serious adverse events in patients with CNCP.

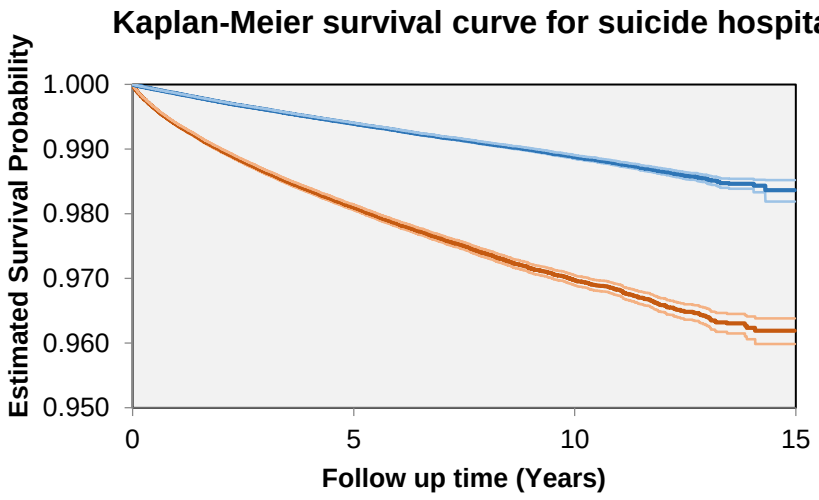


Number of patients at risk

Gabapentinoid users			
655,141	218,454	42,363	0
Gabapentinoid non-users			
2,676,333	829,668	127,930	0

Log-rank test: P<0.001

(a) Fracture hospitalisation



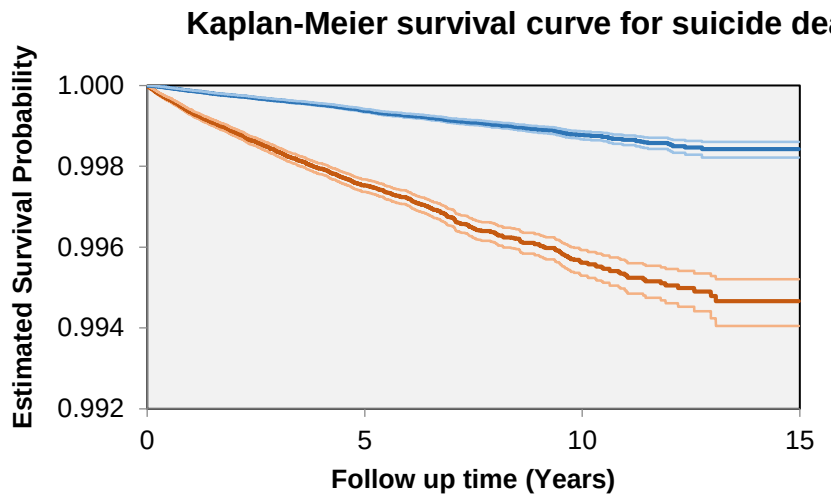
Number of patients at risk

Gabapentinoid users			
655,141	222,477	44,058	0
Gabapentinoid non-users			
2,676,333	843,513	132,286	0

Log-rank test: P<0.001

(b) Suicide hospitalisation

(Continued in the next page)

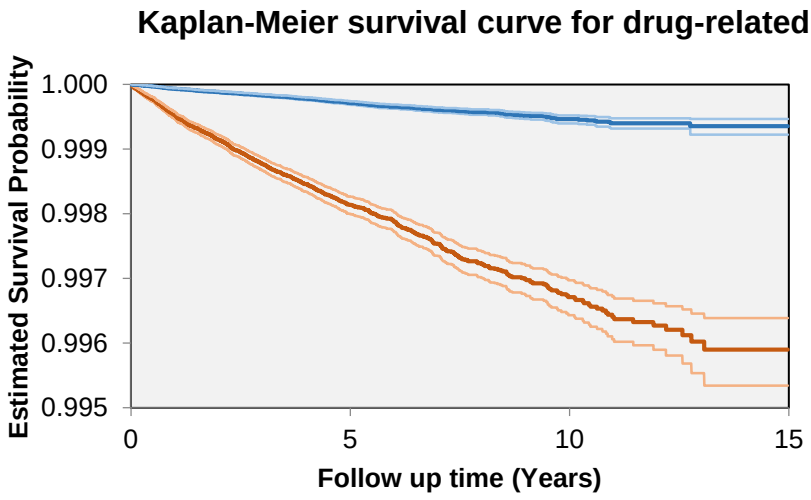


Number of patients at risk

Gabapentinoid users			
655,141	226,096	45,097	0
Gabapentinoid non-users			
2,676,333	846,890	133,162	0

Log-rank test: P<0.001

(c) Suicide death



Number of patients at risk

Gabapentinoid users			
655,141	226,217	45,115	0
Gabapentinoid non-users			
2,676,333	847,025	133,177	0

Log-rank test: P<0.001

(d) Drug-related death

Figure 7-2. Kaplan-Meier survival curves and log-rank test results for the serious adverse events in patients with CNCP

7.4.4. Association between gabapentinoid exposure and serious adverse events

Among the studied serious adverse events, gabapentinoid exposure increases the risk of drug-related death the most (aHR: 3.70, 95% CI: 3.29, 4.16). After considering the baseline influential factors, exposure to gabapentinoids is associated with a significantly higher risk of suicide hospitalisation (aCHR: 1.86, 95% CI: 1.80, 1.91) and suicide death (aHR: 2.35, 95% CI: 2.15, 2.56) compared to those not exposed to gabapentinoids in the CNCP population. Gabapentinoid exposure slightly increases the risk of fracture hospitalisation (aHR: 1.11, 95% CI: 1.09, 1.13) compared to those who were not exposed to gabapentinoids. The log-log plots suggest the models obey the proportional hazards assumption.

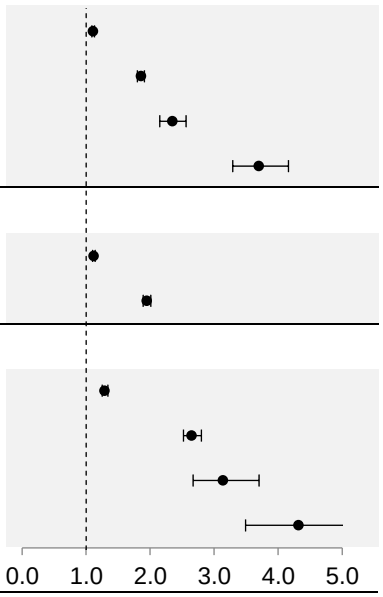
Excluding patients who had a fracture hospitalisation or suicide hospitalisation before the index date, as investigated in sensitivity analysis 1, did not substantially change the effect of gabapentinoid exposure on fracture hospitalisation and suicide hospitalisation, compared to the primary analyses (Table 7-3). This indicates that the results of the primary analysis are not noticeably biased by these non-independent events. Only following patients for 365 days from the index date, as investigated in sensitivity analysis 2, results in higher aHRs/aCHRs for gabapentinoid's association with serious adverse events. This indicates that gabapentinoids have a stronger effect on the risk of serious adverse events that occur closer to the exposure (Table 7-3).

Most of the included baseline comorbidities and baseline pain medications are associated with a higher risk of serious adverse events (Appendix 6), except baseline weak opioid use, which is associated with a significantly lower risk of drug-related death (aHR: 0.86, 95% CI: 0.77, 0.96). Baseline alcohol use problems and

baseline psychoactive substance misuse are the strongest influential factors among the adjusted confounding factors for all the serious adverse events (Appendix 6). For example, for drug-related death, baseline psychoactive substance misuse has an aHR of 13.03 (95%CI: 11.18, 15.20), while baseline alcohol use problem has an aHR of 3.38 (95% CI: 2.74, 4.17). For suicide death, baseline psychoactive substance misuse increases the risk of suicide death by 8.77 times (95% CI: 7.58, 10.15) compared to patients without a psychoactive substance misuse history, and baseline alcohol use problems are also strongly associated with suicide death (aHR: 3.90, 95% CI: 3.27, 4.66).

Table 7-3. Association between gabapentinoid exposure and serious adverse events

	HR/CHR (95% CI)	aHR/aCHR (95% CI)	aHR/aCHR (95% CI)
Primary analysis			
Fracture hospitalisation	1.42 (1.40, 1.44)*	1.11 (1.09, 1.13)*	
Suicide hospitalisation	3.15 (3.07, 3.23)*	1.86 (1.80, 1.91)*	
Suicide death	3.98 (3.68, 4.29)*	2.35 (2.15, 2.56)*	
Drug-related death	6.66 (6.02, 7.38)*	3.70 (3.29, 4.16)*	
Sensitivity analysis 1			
Fracture hospitalisation	1.42 (1.40, 1.44)*	1.12 (1.10, 1.14)*	
Suicide hospitalisation	3.15 (3.07, 3.23)*	1.95 (1.89, 2.01)*	
Sensitivity analysis 2			
Fracture hospitalisation	1.68 (1.63, 1.73)*	1.29 (1.25, 1.34)*	
Suicide hospitalisation	4.50 (4.30, 4.71)*	2.65 (2.52, 2.80)*	
Suicide death	5.00 (4.32, 5.79)*	3.14 (2.67, 3.70)*	
Drug-related death	7.19 (5.93, 8.72)*	4.32 (3.49, 5.35)*	



Notes: (1) HR: crude hazard ratio; aHR: adjusted hazard ratio; CHR: crude cause-specific hazard ratio; aCHR: adjusted cause-specific hazard ratio; (2) The table presents the association between gabapentinoid exposure and the risk of serious adverse events, after adjusting for the baseline demographics, baseline comorbidities and baseline pain medication use. (3) Sensitivity analysis 1 removed patients who had previous hospitalisation from the cohort, which excluded 6,025 patients from the fracture hospitalisation analysis and 2,907 patients from the suicide hospitalisation analysis. Sensitivity analysis 2 only followed patients for 1 year after the index date.

7.5. Discussion

This study identifies a higher incidence rate of the serious adverse events in gabapentinoid users compared to non-users in the CNCP population, where the risk of drug-related death is substantially higher in gabapentinoid users than gabapentinoid non-users. The estimated survival probabilities of the serious adverse events are high in the 15 years after the index date. However, gabapentinoid exposure is significantly associated with a higher risk of the serious adverse events in the CNCP population, especially drug-related death. Baseline psychoactive substance misuse and baseline alcohol use problems are strong influential factors associated with a higher risk of the serious adverse events.

This is the first study to estimate the incidence rates of serious adverse events in gabapentinoid users with CNCP and compare them with gabapentinoid non-users. There is currently no available incidence rate for suicide hospitalisation in the general population or in patients with CNCP, so no comparison can be made to the general population. However, the incidence rates of drug-related death (IR: 0.36, 95% CI: 0.34, 0.39) and suicide death (IR: 0.48, 95% CI: 0.46, 0.51) for gabapentinoid users with CNCP are significantly higher than the national incidence rates, which are 0.08 per 1,000 people for drug-related death and 0.11 per 1,000 people for suicide death (for England and Wales in 2021, according to ONS reports) [181, 253]. The incidence rates of drug-related death (IR: 0.06, 95% CI: 0.05, 0.06) and suicide death (IR: 0.12, 95% CI: 0.12, 0.13) for gabapentinoid non-users are consistent with the national incidence rates, indicating a diagnosis of CNCP does not alter the risk of drug-related death or suicide-death. Thus, the higher than general incidence rates in gabapentinoid users may be attributable to gabapentinoid exposure. Jennison *et al.* (2019) estimated the incidence rate of fracture hospitalisation in England to be between 4.45 and 5.08 per 1,000 population per year between 2004 and 2014 using the HES database [254]. Both gabapentinoid

users (IR: 8.92, 95% CI: 8.81, 9.04) and non-users (IR: 6.23, 95% CI: 6.18, 6.28) in the CNCP population have a higher incidence rate of fracture hospitalisation than the national rate, suggesting that chronic pain and gabapentinoid exposure may both lead to a higher risk of fracture hospitalisation.

The association between gabapentinoid exposure and serious adverse events has not been evaluated before among the CNCP population in England, but other studies have found similar results investigating the association for other populations, or for particular drug utilisation patterns. Jetté *et al.* (2011) conducted a case-control study using the Population Health Research Data Repository from Manitoba, Canada to investigate the association between antiepileptic and non-traumatic fractures in people over 50 years old between 1996 and 2004 [255]. The study found gabapentin exposure in the four months before the fracture was significantly associated with non-traumatic fractures (aOR: 1.49, 95% CI: 1.10-2.02) [255], which supports this study. However, the study only accounted for the confounding effect of demographics and comorbidities (such as epilepsy, diabetes, hypertension, chronic obstructive pulmonary disease, substance use, depression, etc.) and did not consider the effect of other fracture-related drugs. In comparison, this study considered use of pain medication, which has been found to be associated with fracture risk in literature. One study in the US found an increased risk of falls in older Medicare patients who had co-prescribed opioids and gabapentinoids [256], and another Medicare study reported a higher risk for fall-related injuries when gabapentinoids were added to an existing opioid regimen [217].

The association between gabapentinoid exposure and suicide has been studied in the general populations of other countries, with conflicting results. In a self-controlled study in Sweden, Molero *et al.* (2019) found that gabapentinoids increased the hazard of suicidal behaviour and deaths from suicide (age-adjusted

HR: 1.26, 95% CI: 1.20, 1.32), and in the subgroup analyses found that pregabalin contributed more to the suicidal outcomes than gabapentin [20]. Patorno *et al.* (2010) conducted a cohort study using data between 2001 and 2006 in the HealthCore Integrated Research Database, and identified a significantly higher risk of suicidal acts for adult gabapentin users (aHR: 1.44, 95% CI: 1.13, 1.83) but not for pregabalin users (aHR: 1.22, 95% CI: 0.61-2.45) [111]. The association between gabapentin and suicide found in previous studies is consistent with this study, while the effect of pregabalin may need more investigation in future studies.

The association between gabapentinoid exposure and drug-related death was evaluated for the first time in this study. Most available studies on drug-related death associated with gabapentinoids are post-modern studies [88, 104, 105, 257, 258], while the few epidemiological studies that investigated the effect of gabapentinoids on drug-related death outcomes mainly focused on opioids. Gomes *et al.* (2017) conducted two nested case-control studies on opioid users in Ontario, Canada, between 1997 and 2013 using administrative databases to study the risk of opioid-related deaths [23]. The studies found that co-prescribing of gabapentin or pregabalin in the 120 days before the opioid-related deaths was significantly associated with increased odds of opioid-related death, and the association had a dose-dependent effect for gabapentinoids [22, 23].

Other than identifying the association between gabapentinoid exposures and the serious adverse events, this study also found a strong effect of baseline psychoactive substance misuse and alcohol use problems on the serious adverse events, probably because they share similar Central Nervous System (CNS) mechanisms leading to drug-related death and suicide [259, 260]. Extra attention should be given to patients who have substance or alcohol use problems before prescribing them gabapentinoids.

The cohort allocation in this study mimics the intention-to-treat (ITT) analysis in RCTs, which ignores events that occur after the cohort allocation, such as noncompliance and loss of follow up [261]. The ITT design has many advantages and has been used in epidemiological studies to investigate the safety of gabapentinoids [111, 262]. However, it has disadvantages, such as conservatively estimating effects and introducing heterogeneity [261], which in this study could be caused by the different lengths of follow-up times among patients, including some very long follow-up times. The sensitivity analysis including only 365 days after the index date was designed to mitigate this problem, and it showed a stronger association between gabapentinoids and the serious adverse events. The results supported the primary analysis and also indicated that the serious adverse events close to the exposure are more attributable to gabapentinoids.

This study has several strengths in studying the risk of the serious adverse events for gabapentinoid users with CNCP. Firstly, it used a large primary care database that covers around 16 million patients in the UK [188], and therefore contains a sufficient sample size for studying comparatively rare outcomes. For example, the minimum number of events per variable that would provide reliable results in a Cox regression ranges between 5 and 20 (as a rule of thumb), and for multivariable Cox regression analyses, 10 is a widely accepted rule of thumb [263]. The serious adverse event which has the fewest cases among those studied was drug-related death, which had 1,593 cases identified in the study cohorts. This provides sufficient statistical power for a maximum of 22 variables (i.e. all the included baseline characteristics) to fit into the Cox regression model. Secondly, it linked the CPRD primary care database to external databases like the HES APC and the ONS Death Registration. Deaths recorded in the CPRD normally do not include information on the cause, while ONS Death Registration provides causes for all deaths. Linking

them provides complete and accurate information for the serious adverse events. Thirdly, this study applied a cohort design that enabled the investigation of four serious adverse events efficiently in one study. Fourthly, in this study, the risk of the serious adverse events is compared between gabapentinoid users and non-users using a variety of methods. The comparison between incidence rates, Kaplan-Meier survival curves and aHRs provides more information regarding the risk of the serious adverse events in gabapentinoid users and non-users with CNCP.

However, there are still some limitations in this study. Firstly, this study used secondary data which is prone to misclassification. For example, the ICD-10 code used for suicide identification does not identify the intention of self-harm, so it may falsely include accidental death from self-harm. Additionally, the recorded prescribing data does not guarantee that patients actually dispensed and took the medications. Secondly, this study applied a single set of confounding factors to several serious adverse events, which may not fully adjust the confounding factors for each event well. For example, the risk of fracture hospitalisation can be influenced by the diagnosis of osteoporosis and rheumatoid arthritis [264, 265], but these factors were not measured and adjusted for in this study. The confounding factors selected in this study are associated with gabapentinoid initiation and are assumed to be general risk factors for the serious adverse events. Although a backward elimination process was applied to identify variables that best fit the serious adverse event, the problem of unmeasured confounding is still present. Therefore, future studies with better confounding adjustments are still worth conducting. Thirdly, the baseline comorbidities and pain medication use were assumed to be constant over the follow-up period in the Cox models, which does not always reflect the actual situation after the index date. Advanced statistical analysis, such as introducing step or continuous functions in a time-dependent Cox

proportional hazard model [266] could be applied in future studies to better adjust for time-varying covariates.

Fourthly, this study treated gabapentinoid exposures equally without considering the dose or duration of the exposure, while previous studies have suggested a potential dose effect in gabapentinoid-related adverse events [101, 267]. Further studies are needed to test the effect of gabapentinoid utilisation patterns on serious adverse events. Fifthly, as patients have to survive from the CNCP diagnosis to the first prescription of gabapentinoids (i.e. immortal time) to be included in the gabapentinoid user cohort, an immortal time bias exists [268]. However, since immortal time bias theoretically biases down the incidence rate of the serious adverse events for gabapentinoid users in this study, the result would not be negated if the immortal time bias is adjusted for.

In summary, this study identified higher incidence rates of the serious adverse events for gabapentinoid users than non-users in the CNCP population, and incidence rates of the serious adverse events for gabapentinoid users are higher than for the general population. Fracture hospitalisation has the highest incidence rate among the four studied serious adverse events in gabapentinoid users, and the incidence rate of drug-related death in gabapentinoid users is over 6 times the incidence rate in non-users. The higher risk of the serious adverse events in gabapentinoid users is associated with gabapentinoid exposure, after considering influential factors such as baseline demographics, comorbidities, and pain medication use. Further study is needed to evaluate the effect of gabapentinoid utilisation patterns on the risk of serious adverse events.

Chapter 8. Gabapentinoid utilisation patterns and their association with serious adverse events in patients with chronic non-cancer pain in English primary care

8.1. Introduction

Previous analysis found that the incidence rates of target serious adverse events are higher in gabapentinoid users than non-users in patients with CNCP. The Cox models (which treated all gabapentinoid exposures equally) found a significant association between gabapentinoid exposure and serious adverse events in patients with CNCP (Chapter 7). However, since the actual use of gabapentinoids could vary between patients, omitting gabapentinoid exposure patterns may bias the risk estimation and interpretation.

Epidemiological studies using patient-level data enable studies on drug utilisation patterns that help identify high-risk utilisation patterns, and thus facilitate rational drug use [269]. Different drug utilisation measures were developed for different study purposes, such as the incidence of drug use, prescribing quality, combination use, and drug adherence (focusing on persistence and implementation) [269]. The selection of drug utilisation measures generally depends on the study purpose and the availability of prescription data.

The high-dose use of gabapentinoids is considered a risk factor for serious adverse events due to the addiction potential of gabapentinoids found in pharmacological studies [14, 15]. A post-mortem study in the US identified a high blood concentration of gabapentin as a potential cause of death [270], indicating problematic high-dose gabapentin use could be associated with deaths.

On the other hand, the concurrent use of gabapentinoids with other drugs affecting the central nervous system (CNS), especially opioids, could also be risky, according to post-mortem studies [107, 108, 270, 271]. A post-mortem study including 3,750 deceased from Coroners' cases in London and South East England between 1 January 2016 and 31 December 2017 found the most common drugs identified with gabapentin (60.2%) and pregabalin (64.6%) were non-heroin opioids [107]. Similarly, another study extracted data from the English National Programme on Substance Abuse Deaths (NPSAD) and found opioids were co-detected in 92.0% of the substance abuse deaths involving gabapentinoids [108]. Moreover, several epidemiological studies found a higher risk of opioid-related death when gabapentinoids are used with opioids [22, 23].

This study hypothesises that some utilisation patterns of gabapentinoids contribute more to the risk of serious adverse events. It further hypothesises that persistent use of gabapentinoids quickly builds up to high-dose use compared to patients treated with gabapentinoids for a short period, hence incurring serious adverse events.

8.2. Aim and objectives

This chapter is a hypothesis-generating and testing study that investigates the utilisation pattern of gabapentinoids in the CNCP population in English primary care and its impact on the risk of serious adverse events. The objectives are:

(1) To identify persistent, high-dose, and concurrent gabapentinoid exposures and persistent, high-dose, and concurrent gabapentinoid users in the CNCP population;

(2) To assess the discontinuation probability (i.e. drug survival) of the first gabapentinoid exposure episode over time in gabapentinoid users with CNCP;

(3) To investigate the association between gabapentinoid high-dose users and the risk of drug-related deaths, fracture hospitalisations, and suicides in gabapentinoid users with CNCP.

8.3. Methods

8.3.1. Study design and data sources

This study is a cohort study of gabapentinoid users with CNCP in the CPRD database linked to external databases between 1 January 2005 and 31 December 2019. The CPRD primary care database was linked to the Office for National Statistics (ONS) Death Registry, the Hospital Episode Statistics (HES) Admitted Patient Care (APC) databases and the ONS Index of Multiple Deprivation 2015.

8.3.2. Study population

The *gabapentinoid user* study cohort is defined as patients with CNCP who were issued at least one gabapentinoid prescription in the follow-up period 1 January 2005 to 31 December 2019 (i.e. the *gabapentinoid user cohort* defined in Chapter 6). The study cohort was followed from the study entry date to the study exit date. The date of the first prescription of gabapentinoids after the study entry date was defined as the *index date* (Figure 8-1). The study cohort is categorised into *high-dose user* and *persistent user* subgroups during the analysis.

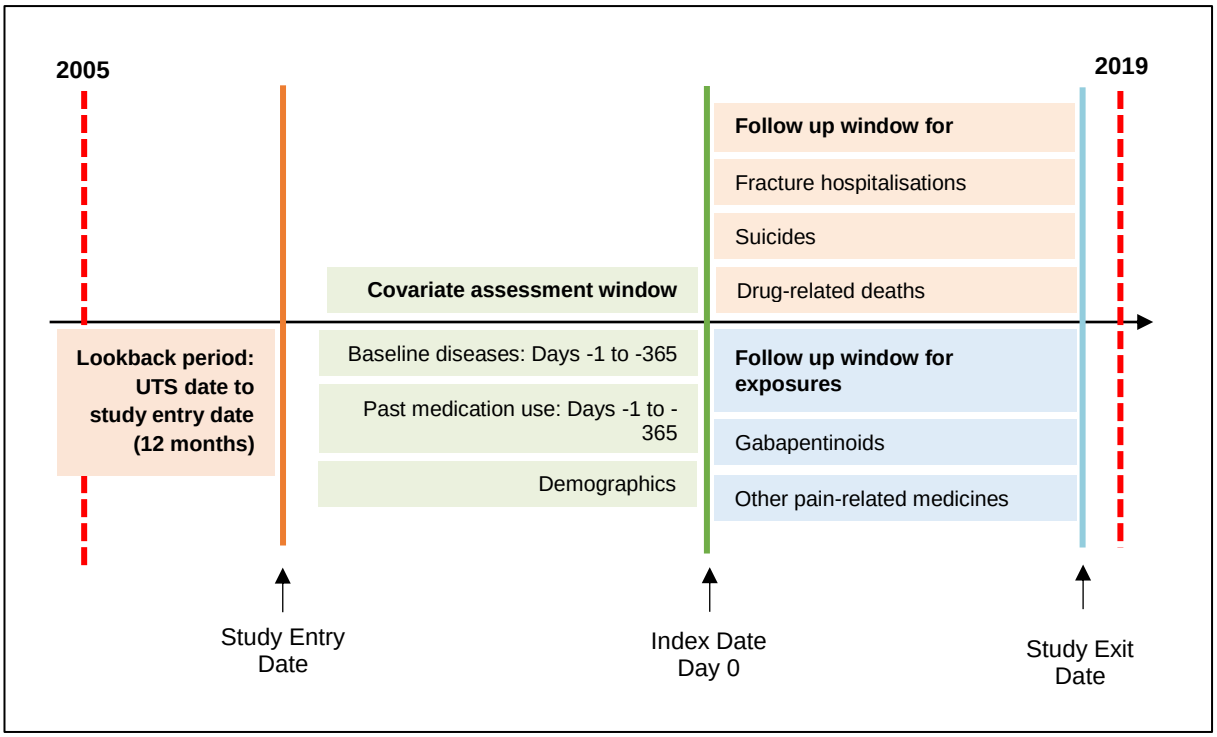


Figure 8-1. Definition of the follow-up period for the cohort study

8.3.3. Measure of gabapentinoid utilisation patterns

Measures for gabapentinoid utilisation patterns in this study are defined as persistent exposure, high-dose exposure, and concurrent exposure (with other pain medications). Prescriptions of any formulation of gabapentinoids, opioids, benzodiazepines, antidepressants, and Z-drugs between the index date and the study exit date were identified using the product code lists generated in Chapter 5 from the therapy files of the CPRD. Included gabapentinoid formulations are capsules, tablets, oral solutions, oral suspensions, and gels. Prescriptions of gabapentinoids were further categorised into gabapentin and pregabalin subgroups. Prescriptions of opioids, benzodiazepines, antidepressants, and Z-drugs were categorised into more detailed subgroups by either pharmacological mechanism or indications (as defined in Section 6.3.3, Chapter 6).

Data preparation

To facilitate the measurement of gabapentinoid utilisation patterns, the days of supply of each gabapentinoid prescription (i.e. the number of days covered by the prescription) and the daily dose of each prescription are needed. Since the ranges of recommended daily doses for gabapentinoids are large (900-3,600 mg for gabapentin and 150-600 mg for pregabalin) [8], no standard daily dose can be assigned to gabapentinoid prescriptions.

There are a variety of variables available in the CPRD prescription datasets (Table 8-1). Although the number of days of supply (the variable named *course duration*) is provided for each prescription, the majority of the prescriptions have a value of 0 in this field, indicating a high rate of missing information for this variable. In comparison, the quantity and daily dose fields have a lower missing information rate. Therefore, a calculated alternative for the days of supply was estimated for the prescriptions by dividing the total quantity (e.g. the number of tablets in the prescription) of drugs prescribed by the daily dose provided in the dosage information (Equation 8-1). However, the quantity and daily dose data need to be cleaned and imputed before this calculation. Thus, an algorithm for data cleaning and imputation is required.

$$Days\ of\ supply\ of\ the\ prescription = \frac{Total\ quantity}{Daily\ dose}$$

Equation 8-1. Calculation for the days of supply of a prescription

The data cleaning process consists of removing outliers that are obviously errors. The outlier threshold for quantity was set as 1,000 for gabapentinoid tablets and capsules and 6,000 for gabapentinoid liquid formulations. The threshold for tablets and capsules was chosen because (1) the 99th percentile of the quantity variable for

gabapentinoid prescriptions is 336 and (2) it allows the highest recommended daily dose to be taken using the smallest tablet/capsule dose for 28 days without being considered an outlier. The threshold for liquid formulations was selected following the same procedure (the 99th percentile is 1,800 ml). There was no implausible outlier observed in the daily dose (the daily dose in the CPRD ranges from 1-9), so no data-cleaning process was needed. Outliers were identified and set to missing in the data cleaning process, ready for the imputation process along with the rest missing data.

After data cleaning, a data imputation process was applied in steps to replace any missing data with reasonable values for gabapentinoid prescriptions. Each missing value was filled in only once, only passing to the next step if no suitable source could be found for the current step. The steps for imputing the missing data were run in the following order:

(1) replace with the nearest (in time) prescription of the same product in the patient;
(2) replace with the nearest prescription of the same substance and formulation in the patient;
(3) replace with the median of all prescriptions of the same product in the study cohort;
(4) replace with the recommended daily dose of the product (for daily dose imputation only).

The start of a prescription is defined as the event date when the prescription was prescribed, assuming patients collect the prescription and take the first dose on the same day as the prescription date. The end of a prescription was defined as the last date covered by the prescription according to the calculated days of supply.

Table 8-1. Prescription-related variables in GOLD therapy and Aurum drug issue data files selected for drug utilisation measure

Content	GOLD	Aurum	Description
Patient identifier	patid	patid	Encrypted unique identifier given to a patient in CPRD GOLD or Aurum
Event date	eventdate	issuedate	Date associated with the event (i.e. prescription)
Entered date	sysdate	enterdate	Date the event was entered into Vision or EMIS Web®
Product Code	prodcode	prodcodeid	CPRD unique code for the treatment selected by the GP. Linkable to lookup files to identify the product and derive the strength.
Quantity	qty	quantity	Total quantity entered by the GP for the prescribed treatment
Course duration	numdays	duration	Duration of the treatment in days
Dosage Identifier	dosageid	dosageid	Identifier that allows the event's dosage information, especially daily dose, on the event to be retrieved.

Persistent gabapentinoid exposure episode

Drug exposure in this study is defined as days that are covered by the prescriptions prescribed during primary care consultations and recorded in the CPRD, making the assumption that patients dispensed and took the medication after being prescribed. A *gabapentinoid exposure episode* is defined as a continuous period covered by the supply days of gabapentinoid prescriptions, with interruptions no longer than 30 days between consecutive prescriptions. For example, a time period covered by two gabapentinoid prescriptions with a gap (defined as the *grace period*) <=30 days is defined as a single episode. Several example scenarios defining gabapentinoid exposure episodes are presented in Figure 8-2.

There are several reasons for allowing a *grace period* in identifying gabapentinoid exposure episodes. Firstly, the non-compliant use of pain medication is common in patients with chronic pain. A systematic review of 25 articles reported the non-adherence rate ranges between 8% and 62% (weighted mean: 40%) in patients with

CNCP [272]. Secondly, 48.3% of all gabapentinoid prescriptions were issued before the end date of a previous prescription, indicating a high rate of overlap. The non-compliant use and overlapping prescriptions make it likely that patients stockpile excess pain medications during the treatment course, and these stockpiles are likely to be used to cover any gaps in the medical record.

The *length of an episode* is defined as the period between the date of the first prescription in the episode and the last day covered by any prescription in the episode. If the end of an episode would be later than the patient's study exit date, the end date of that episode is replaced by the study exit date. Episodes over six months long are defined as *persistent episodes*, while episodes over 12 months long are categorised as a subgroup of persistent episodes and defined as *extended persistent episodes*. Patients who had one or more *persistent episodes* (any type) are defined as *persistent users*.

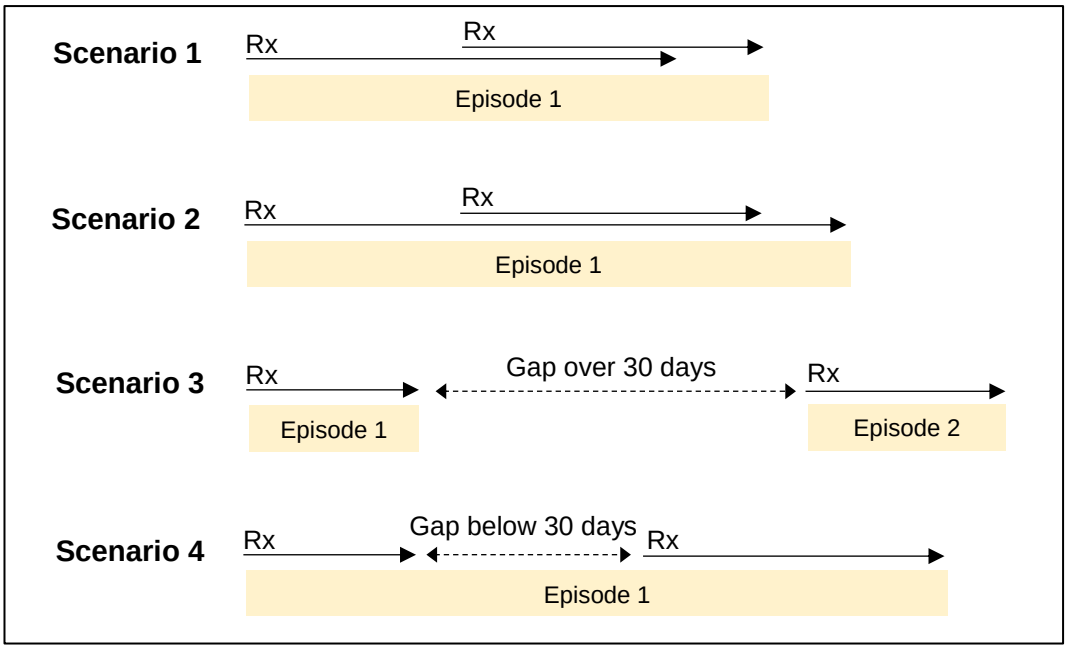


Figure 8-2. Example scenarios illustrating the definitions of a gabapentinoid exposure episode

Note: In Scenario 1, the two prescriptions are measured as one episode, where the end of the episode is the end of the later prescription. In Scenario 2, the two prescriptions are measured as one episode, but the end of the episode is the end of the earlier prescription, as this is later than the end of the later prescription. In Scenario 3, the gap between the closest two prescriptions is longer than 30 days, so they are measured as two separate episodes. In Scenario 4, the gap between the closest two prescriptions is less than 30 days, so they are measured as one single episode, with the start of the episode being the date of the earlier prescription's index date and the end being the last date covered by the later prescription.

High-dose gabapentinoid exposure episode

The *average daily dose* of each gabapentinoid exposure episode is measured in units of Defined Daily Dose (DDD) so that gabapentin and pregabalin daily doses are comparable. A *high-dose gabapentinoid exposure episode* is defined as a gabapentinoid exposure episode with an average daily dose over the BNF maximum recommended daily dose (gabapentin >3600 mg/day (2 DDD/day), pregabalin > 600 mg/day (2 DDD/day)) [8]. Patients with one or more high-dose episodes of gabapentinoid exposure were defined as *high-dose users.*

The total DDDs contained in one prescription is calculated by multiplying the item quantity (e.g. the number of tablets) by the unit dose of the drug (e.g. 300 mg/tablet) and then dividing it by the DDD of the drug (1800 mg for gabapentin or 300 mg for pregabalin). The average daily dose for an episode (DDD/day) is calculated by summing up the DDDs of all prescriptions in that episode and dividing this by the length of the episode in days (Equation 8-2).

$$Average\ daily\ DDD = \sum_{i=1}^{n} \frac{Quantity_i \times Unit\ dose_i}{Drug\ DDD_i \times Length\ of\ the\ episode}$$

Where i is the prescription number and n is the number of prescriptions in the episode.

Equation 8-2. The calculation of the average daily dose of a gabapentinoid exposure episode

Concurrent exposure

A *concurrent exposure* is any exposure with an overlapping exposure of *other pain medications.* This overlap occurs if any prescription of *other pain medications* is prescribed within the *overlap time window*, which starts before the beginning of the gabapentinoid exposure episode and finishes at the end of the gabapentinoid exposure episode (Figure 8-3).

Other pain medications are defined as opioids, benzodiazepines, antidepressants, and Z-drugs and their subcategories, and identified in the same way as *pain medications* in Chapter 6 (Section 6.3.3). These pain medications are selected because they are commonly used to manage pain and pain-related symptoms, and the combination use of gabapentinoids and these medications (especially opioids) are risk factors for serious adverse events.

The *overlap time window* has a different start date for each category of pain medication. Because antidepressants are often repeatedly prescribed to control chronic pain-related mental symptoms, it is assumed they are prescribed with 28 days of supply, following the NHS 28-day repeat prescribing policy [273]. Thus, the *overlap time window* for antidepressants starts 28 days before the gabapentinoid exposure start date, meaning any prescription of antidepressants within 28 days of the start of a gabapentinoid exposure episode will have at least 1 day of overlap with that gabapentinoid exposure episode and form a concurrent exposure. The recommended maximum duration of benzodiazepine and z-drug prescriptions is 2-4 weeks, so the *overlap time window* for these drugs starts 14 days before the gabapentinoid exposure start date to allow for the detection of concurrent exposures [274, 275]. Similarly, opioids are not recommended for long-term use in chronic pain and are recommended to be prescribed for no longer than the expected duration of the severe pain that warranted opioid therapy [276]. Therefore, the *overlap time window* for opioids begins 3 days before the gabapentinoid exposure start date to identify concurrent exposure.

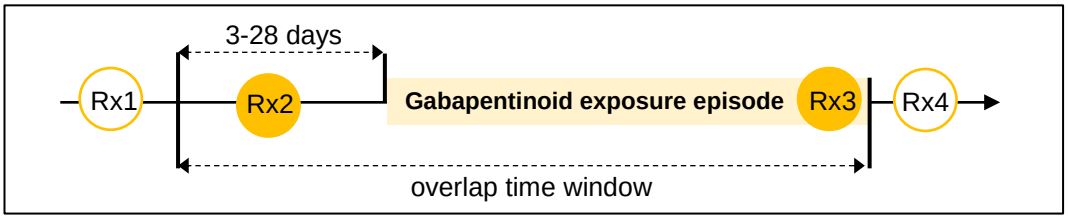


Figure 8-3. Definition of concurrent exposure to pain-related drugs

Note: Above are four example prescriptions of other pain medications (Rx1, Rx2, Rx3 and Rx4 mark the start of each prescription) around one gabapentinoid exposure episode. Rx2 is prescribed within the overlap time window, so its exposure period is likely to overlap with the gabapentinoid exposure episode. In contrast, Rx1 is prescribed outside the overlap time window, so is not likely to overlap with the gabapentinoid exposure episode. Rx3 is prescribed during the gabapentinoid exposure episode, so it overlaps with the gabapentinoid exposure episode. Rx4 is prescribed after the end of the gabapentinoid exposure episode, so it does not overlap with the gabapentinoid exposure episode. Therefore, Rx1 and Rx4 are not concurrent exposures, but Rx2 and Rx3 are concurrent exposures.

8.3.4. Outcome measures

Serious adverse events

The serious adverse events are defined as fracture hospitalisations, suicide hospitalisations, suicide deaths, and drug-related deaths. Serious adverse events that occur between the index date and the study exit date (Figure 8-1) are identified using ICD-10 codes from the HES APC and ONS Death Registration databases as described in Chapter 7 (Section 7.3.3).

Baseline characteristics

The baseline characteristics are defined as the baseline demographics (age, gender, IMD decile), baseline comorbidities (alcohol use problems, anxiety, depression, diabetes, COPD, CKD, epilepsy, and psychoactive substance misuse) and baseline pain medication use (opioids, benzodiazepines, antidepressants, and Z-drugs) in the 12 months before the index date. The identification process of the baseline characteristics is described in Chapter 6 (Section 6.3.3).

8.3.5. Analytical methods

Descriptive statistics are used to report patients' baseline demographics and gabapentinoid utilisation patterns. Patients' gender, baseline comorbidities, baseline pain medication use, and gabapentinoid utilisation patterns are reported as numbers and percentages. Patients' age, time to initiation of gabapentinoids, follow-up time from the index date to the study exit date, days of supply of gabapentinoid prescriptions, and length and the average daily dose of gabapentinoid exposure episodes are reported as mean values with the standard deviation (SD). The IMD decile is reported as a median and interquartile range (IQR).

The time to discontinuation of the first gabapentinoid exposure episode was evaluated using the Kaplan-Meier estimator to investigate how many gabapentinoid users remain on gabapentinoid treatment over time. The Kaplan-Meier estimator estimates the probability of patients continuing exposure to gabapentinoids after the index date [277]. The event in the drug survival analysis is defined as the discontinuation of the first gabapentinoid exposure episode. The *grace period* for identifying the first gabapentinoid exposure episode in the primary drug survival analysis is 30 days. Since the Kaplan-Meier technique for drug survival is sensitive to the *grace period* length, sensitivity analyses were also conducted on *grace periods* of 14, 60, and 90 days, allowing for patients with CNCP to have highly irregular prescription or stockpiling behaviours due to their chronic condition [278]. In a subgroup analysis, the Kaplan-Meier estimator was applied to the subgroups of *high-dose gabapentinoid users* and *non-high-dose gabapentinoid users* (anyone in the study cohort who is not a *high-dose gabapentinoid user*). A log-rank test was applied in the subgroup analysis to test for differences in the time to discontinuation of the first gabapentinoid exposure episode between *high-dose* and *non-high-dose* gabapentinoid users.

The Kaplan-Meier survival curves with the 95% confidence interval (CI) bands and the number of patients at risk at certain follow-up time points are presented for the discontinuation of the first gabapentinoid exposure episode. The median survival time, defined as the time by which half of the study cohort had discontinued the first gabapentinoid exposure episode, was reported with a 95% CI. The annual survival probability of the first gabapentinoid exposure episode was reported for five years after the index date with 95% CI. The P value of the log-rank test was reported.

A Cox proportional hazard model with gabapentinoid utilisation patterns set as time-varying covariates was applied to study the association between high-dose

gabapentinoid exposure and the risk of the serious adverse events in gabapentinoid users with CNCP [266]. The associations between high-dose gabapentinoid exposure and fracture hospitalisations, suicide hospitalisations, suicide deaths, and drug-related deaths were tested in four separate Cox proportional hazard models. The confounding factors adjusted for in the models include baseline characteristics (demographics, comorbidities, and pain medication use) and the effect of persistent gabapentinoid exposure. The baseline characteristics were fitted into the Cox model as binary time-invariant variables, while high-dose and persistent gabapentinoid exposures were fitted as binary time-varying variables. This is because the baseline characteristics are assumed to be constant over the follow-up period, but the persistent and high-dose gabapentinoid exposure variables do not follow this assumption and change over the follow-up period [266].

Backward elimination was applied for covariate selection [226]. A log-log plot of the covariates against survival time was applied to test the proportional hazard assumption [249]. The hazard ratios (HRs) generated in univariable models, and the adjusted hazard ratios (aHRs) generated in multivariable models were reported with 95% CI for high-dose gabapentinoid exposure for the serious adverse events. Forest plots were presented for the aHRs. All the statistical analyses were conducted in STATA v14 (Stata-Corp, Texas, USA, 2015).

8.4. Results

8.4.1. Cohort selection and baseline characteristics

Of the 655,141 gabapentinoid users with CNCP, over a third were persistent gabapentinoid users who were exposed to at least one persistent gabapentinoid exposure episode during the follow-up period (n=250,949, 38.3%) while a small

percentage were high-dose gabapentinoid users who were exposed to at least one high-dose gabapentinoid exposure episode (n=13,674, 2.1%) (Figure 8-4).

The baseline characteristics of the *gabapentinoid persistent user* subgroups have a lower proportion of females than the *gabapentinoid user cohort* (37.3% vs. 62.7%), but are otherwise similar (Table 8-2). However, the *high-dose user* subgroup shows some noticeable differences in baseline characteristics. *Gabapentinoid high-dose users* are younger at the initiation of gabapentinoids (48.86 vs. 55.91 years) and are more deprived (median IMD: 7 vs. 9). They also have higher baseline alcohol use problems (1.6%) and psychoactive substance misuse (4.7%) compared to the *gabapentinoid user* cohort.

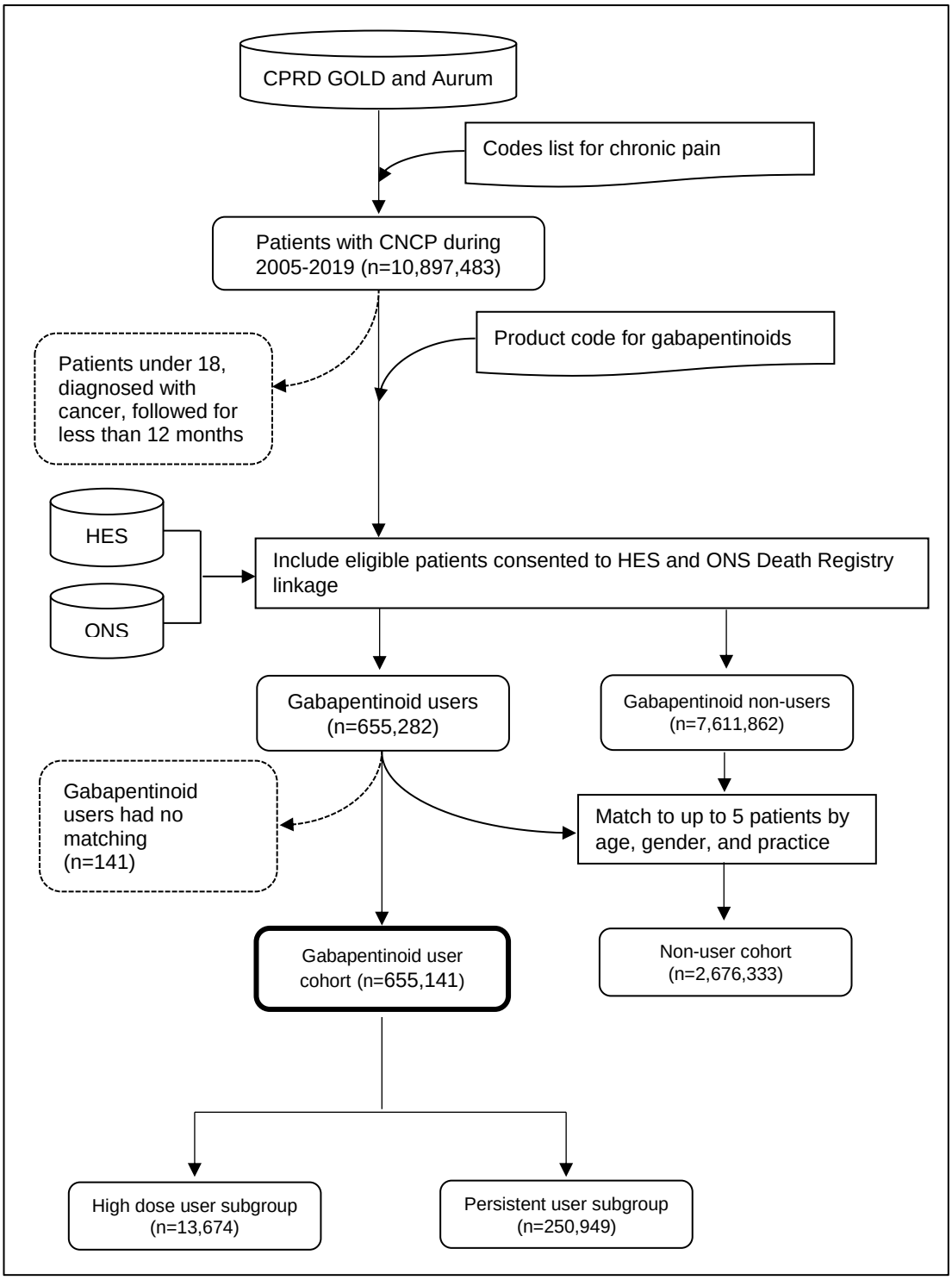


Figure 8-4. Flow chart for generating the study cohorts and sub-cohorts

Note: The box in bold is the study cohort of this study.

Table 8-2. Demographics of the study cohorts and sub-cohorts

	GPN users	Persistent users	High dose users
Baseline demographics			
Number of users (% of GPN users)	655,141	250,949 (38.3%)	13,674 (2.1%)
Mean age at index date (SD)	55.91 (16.23)	56.32 (15.64)	48.86 (13.25)
Number of females (%)	411,066 (62.7%)	93,583 (37.3%)	6,394 (46.8%)
Mean time to initiation[1] (SD)	4.36 (3.88)	3.80 (3.71)	2.13 (2.84)
Mean follow-up time[2] (SD)	4.22 (3.25)	4.99 (3.27)	5.89 (3.71)
Median IMD index (IQR)	6 (3,8)	6 (4,9)	7 (4,9)
Baseline demographics (N, %)			
Mental health disorder	108,273 (16.5%)	48,929 (19.5%)	3,415 (25.0%)
Depression	81,388 (12.4%)	37,865 (15.1%)	2,670 (19.5%)
Anxiety	52,707 (8.0%)	23,231 (9.3%)	1,622 (11.9%)
Diabetes	66,523 (10.2%)	30,259 (12.1%)	1,574 (11.5%)
CKD	14,849 (2.3%)	6,227 (2.5%)	147 (1.1%)
COPD	21,964 (3.4%)	9,323 (3.7%)	381 (2.8%)
Epilepsy	8,080 (1.2%)	4,612 (1.8%)	355 (2.6%)
Psychoactive substance misuse	4,691 (0.7%)	2,631 (1.0%)	646 (4.7%)
Alcohol use problem	3,716 (0.6%)	1,921 (0.8%)	214 (1.6%)
Baseline pain medication use (N, %)			
Any opioids	369,846 (56.5%)	134,258 (53.5%)	6,677 (48.8%)
Strong opioids	167,231 (25.5%)	68,578 (27.3%)	4,084 (29.9%)
Weak opioids	293,679 (44.8%)	102,308 (40.8%)	4,605 (33.7%)
Any antidepressants	305,935 (46.7%)	113,817 (45.4%)	5,491 (40.2%)
TCAs	202,310 (30.9%)	73,907 (29.5%)	3,480 (25.4%)
MAOIs	267 (0.0%)	113 (0.0%)	6 (0.0%)
SSRIs	120,145 (18.3%)	46,166 (18.4%)	2,171 (15.9%)
SNRIs	24,902 (3.8%)	11,343 (4.5%)	725 (5.3%)
Any benzodiazepines	89,225 (13.6%)	32,563 (13.0%)	2,023 (14.8%)
Hypnotics	14,790 (2.3%)	6,139 (2.4%)	443 (3.2%)
Anxiolytics	77,879 (11.9%)	27,958 (11.1%)	1,728 (12.6%)
Any Z-drugs	40,830 (6.2%)	16,804 (6.7%)	1,098 (8.0%)

Note: CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; TCA: Tricyclic antidepressant; MAOI: Monoamine Oxidase Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Noradrenaline Reuptake Inhibitor; 1. Mean time from the study entry date to the initiation of gabapentinoid (i.e., first valid gabapentinoid prescription); 2. Mean follow-up time from the index date to the study exit date

8.4.2. Drug utilisation pattern of gabapentinoids

During the study period (1 January 2005 to 31 December 2019), 13,314,692 gabapentinoid prescriptions (gabapentin n=7,409,297; pregabalin n=5,905,395) were issued to 655,141 gabapentinoid users, for which 1,457,802 episodes of gabapentinoid exposure were identified (Table 8-3). On average, 20.32 prescriptions and 2.23 episodes of gabapentinoid exposure were attributed to each gabapentinoid user, and each patient-year contained 2.37 prescriptions and 0.26 exposure episodes on average.

The median days of supply for gabapentinoid prescriptions is 28 days, and this remains unchanged if prescriptions of gabapentin and pregabalin are considered separately (Table 8-3). Considering the small SD of the days of supply, gabapentinoid prescriptions are most likely to be prescribed to patients with CNCP on a 28-day basis. In contrast, the length of gabapentinoid exposure episodes is much more unevenly distributed, with a mean of 223.62 days (SD: 440.34) and a median of 63 days (IQR: 34, 193), indicating that some gabapentinoid exposure episodes are very long. The average daily dose of gabapentinoid exposure episodes is 0.57 DDD/day (SD: 0.52), which is close to the lower end of recommended daily dose for gabapentinoids (0.5-2.0 DDD/day).

Table 8-3. Characteristics of gabapentinoid prescriptions and exposure episodes

Gabapentinoid prescriptions	
Number of gabapentinoid prescriptions	13,314,692
Number of gabapentin prescriptions (%)	7,409,297 (55.6%)
Number of pregabalin prescriptions (%)	5,905,395 (44.4%)
Mean days of supply of gabapentinoid prescriptions (SD)	30.44 (0.22)
Median days of supply of gabapentinoid prescriptions (IQR)	28 (14,33)
Mean days of supply of gabapentin prescriptions (SD)	33.23 (24.42)
Median days of supply of gabapentin prescriptions (IQR)	28 (19, 33)
Mean days of supply of pregabalin prescriptions (SD)	26.93 (0.18)
Median days of supply of pregabalin prescriptions (IQR)	28 (14, 28)
Gabapentinoid exposure episodes	
Number of gabapentinoid exposure episodes	1,457,802
Mean length (days) of the gabapentinoid exposure episodes (SD)	223.62 (440.34)
Medan length (days) of the gabapentinoid exposure episodes (IQR)	63 (34,193)
Mean average daily dose (DDD/day) of gabapentinoid exposure episodes (SD)	0.57 (0.52)
Median average daily dose (DDD/day) of gabapentinoid exposure episodes (IQR)	0.49 (0.23, 0.67)

Of the 1,457,802 gabapentinoid exposure episodes, 26.3% lasted over six months and 15.3% lasted over 12 months. Around 1.6% of the gabapentinoid exposure episodes were high-dose episodes (Table 8-4). Over half of the gabapentinoid exposure episodes had concurrent exposure to opioids (n=733,153, 50.3%), of which most concurrently prescribed were weak opioids (n=465,330, 31.9%). Similarly, a high percentage of gabapentinoid exposure episodes included concurrent exposure to antidepressants (n=660,508, 45.3%).

Of the 655,141 gabapentinoid users, 38.3% (n=250,949) ever had persistent and 2.1% (n=13,674) ever had high-dose exposure to gabapentinoids. Amongst the 250,950 persistent users, 68.9% (n=172,920) had ever got gabapentinoid exposure episodes over 12 months. Furthermore, around 1.8% (n= 11,983) of gabapentinoid users had ever got both persistent and high-dose gabapentinoid exposure. Over half of gabapentinoid users were concurrently exposed to gabapentinoids and opioids at least once (n=370,413, 56.5%), while around half were concurrently

exposed to gabapentinoids and antidepressants at least once (n=321,865, 49.1%) (Table 8-4). More gabapentinoid users had concurrent exposure to weak opioids (n=266,207, 40.6%) than strong opioids (n=212,490, 32.4%). Of the antidepressant subgroups, more gabapentinoid users were concurrently prescribed TCAs with gabapentinoids (n=185,288, 28.3%). The number of gabapentinoid users who were concurrently exposed to benzodiazepines (n=104,291, 15.9%) or Z-drugs (n=57,895, 8.8%) at least once are comparatively low.

Table 8-4. Gabapentinoid utilisation patterns at exposure episode and patient levels

	Exposure episode	**Patient**
Number (N)	1,457,802	655,141
Persistent gabapentinoid exposure (N, %)		
Persistent >6 months	383,361 (26.3%)	250,949 (38.3%)
Extended persistent >12 months	222,965 (15.3%)	172,920 (26.4%)
High-dose gabapentinoid exposure (N, %)		
High dose	23,380 (1.6%)	13,674 (2.1%)
Concurrent exposure (N, %)		
Concurrent with any opioid	733,153 (50.3%)	370,413 (56.5%)
Concurrent with strong opioids	403,854 (27.7%)	212,490 (32.4%)
Concurrent with weak opioids	465,330 (31.9%)	266,207 (40.6%)
Concurrent with any benzodiazepine	156,390 (10.7%)	104,291 (15.9%)
Concurrent with hypnotics	30,336 (2.1%)	17,645 (2.7%)
Concurrent with anxiolytics	132,142 (9.1%)	92,298 (14.1%)
Concurrent with any antidepressant	660,508 (45.3%)	321,865 (49.1%)
Concurrent with SSRIs	305,330 (20.9%)	154,363 (23.6%)
Concurrent with SNRIs	97,137 (6.7%)	55,947 (8.5%)
Concurrent with TCAs	334,444 (22.9%)	185,288 (28.3%)
Concurrent with MAOIs	578 (0.0%)	311 (0.0%)
Concurrent with any Z-drug	91,004 (6.2%)	57,895 (8.8%)

8.4.3. Drug survival analysis of gabapentinoid episodes

The Kaplan-Meier survival curves show the estimated survival probability of the discontinuation of the first gabapentinoid exposure episode over the follow-up

period in patients with CNCP (Figure 8-5). The survival curve for the primary analysis dropped rapidly after the index date, with a median survival time of 60 days (95% CI: 60, 61), meaning half of gabapentinoid users with CNCP discontinue their first gabapentinoid exposure episode within 60 days of initiation. However, the curve flattened after the initial drop, with a survival probability of 0.19 (95% CI: 0.19, 0.19), 0.10 (95% CI: 0.09, 0.10) and 0.06 (95% CI: 0.06, 0.06) at the end of year 1, year 3, and year 5 respectively (Table 8-5). This means around 19% of gabapentinoid users with CNCP continued their first gabapentinoid exposure episode at least 1 year after the index date, and some continued the first gabapentinoid exposure episode until at least year 5.

The sensitivity analyses illustrated that the Kaplan-Meier drug survival analysis is sensitive to the grace period. A 14-day grace period shortened the median survival time to 44 days (95 CI: 44, 45), while the 60-day and 90-day grace periods extended the median survival time to 78 days (95% CI: 77, 78) and 79 days (95% CI: 78, 80) respectively (Table 8-5). The difference between 60-day and 90-day grace periods is small; indicating the measure of gabapentinoid exposure episodes becomes more consistent when the grace period is set to over 60 days (Table 8-5).

In the subgroup analysis, the survival probability is higher for *high-dose gabapentinoid users* than for *non-high-dose users* over the follow-up period (Figure 8-6). The median survival time of the *high-dose users* is 360 days (95% CI: 345, 375), but this value is only 58 days (95% CI: 58, 59) for *non-high-dose users*. By the end of the first year after the index date, half of the *high-dose users* were still on their first gabapentinoid exposure episode. In contrast, only 19% (95% CI: 0.18, 0.19) of *non-high-dose users* were still on their first gabapentinoid exposure episode at the end of year 1. The survival probability remained higher for *high-dose gabapentinoid users* in the following years of the follow-up period (Table 8-5).

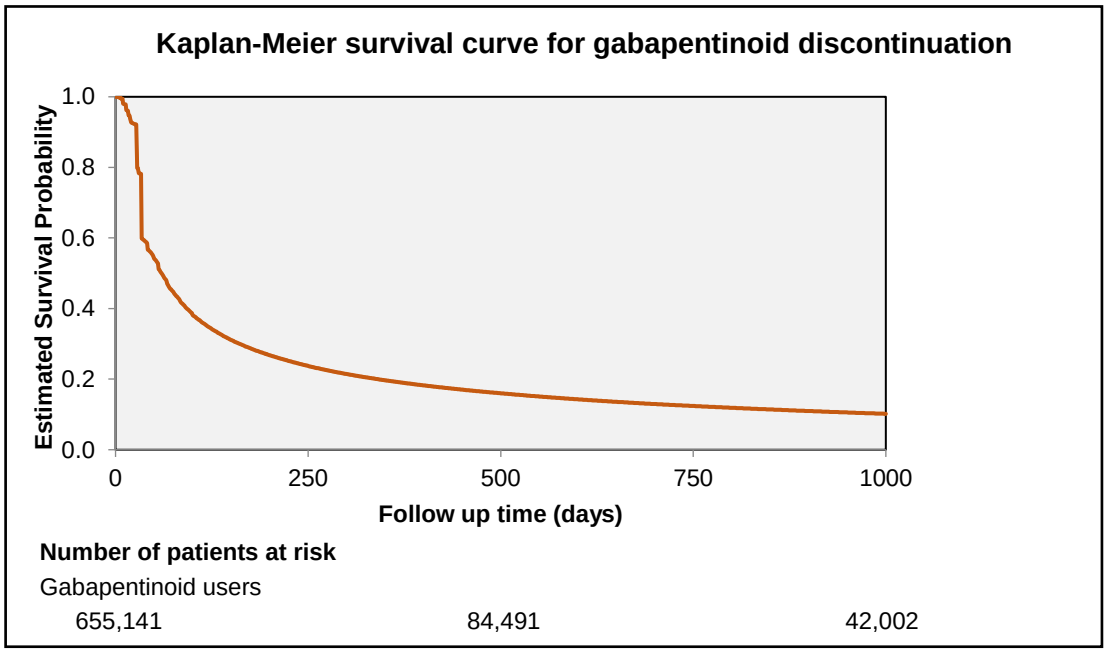


Figure 8-5. Kaplan-Meier survival curve for the primary analysis of the discontinuation of the first gabapentinoid exposure episode

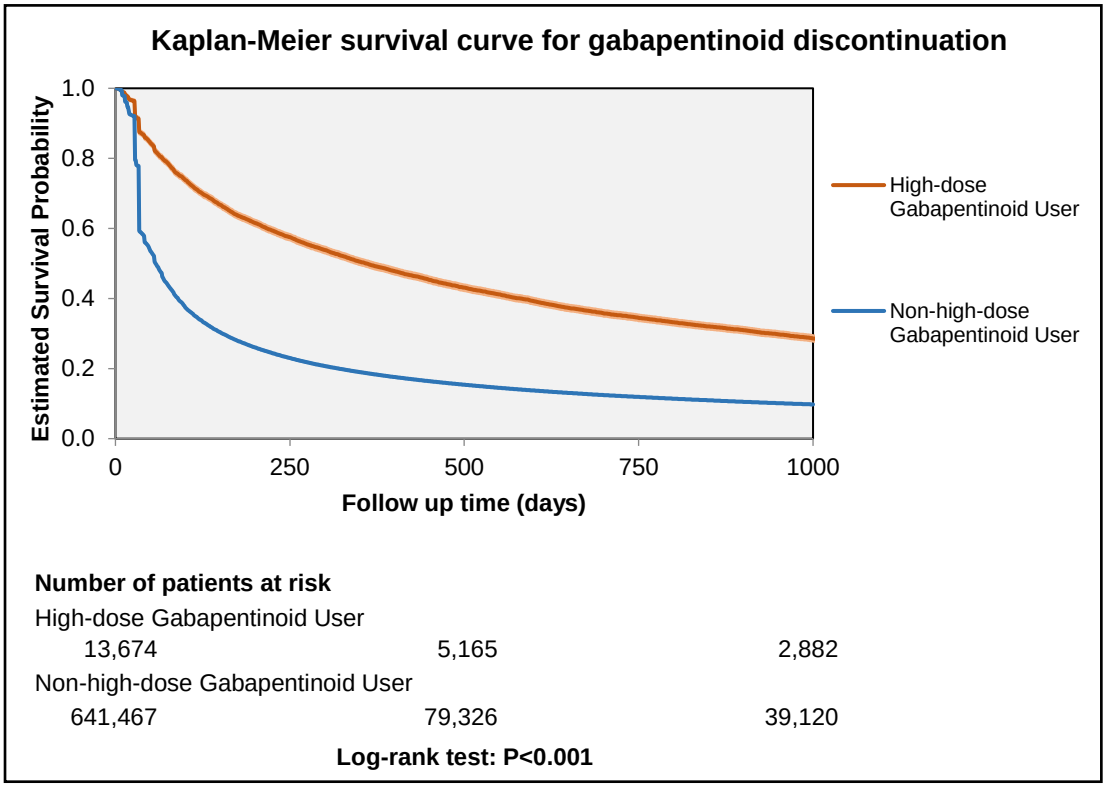
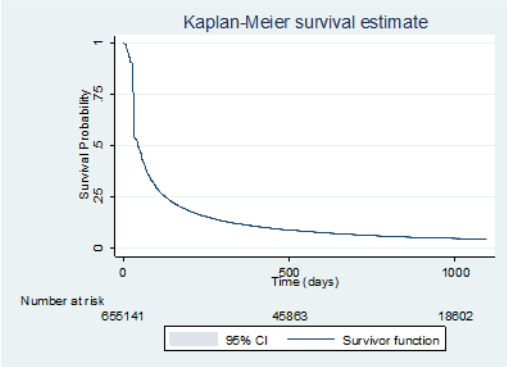
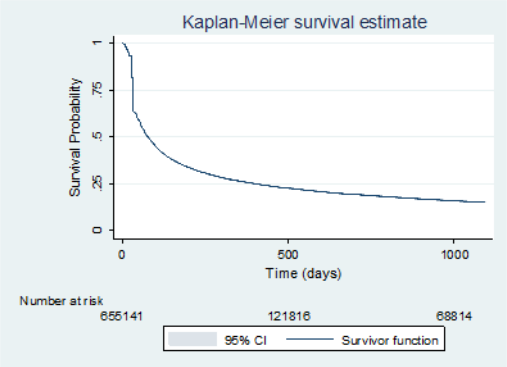


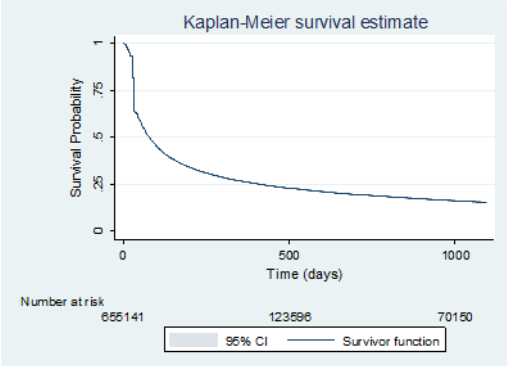
Figure 8-6. Kaplan-Meier survival curves for the subgroup analysis of the discontinuation of the first gabapentinoid exposure episode



a) 14-day grace period



b) 60-day grace period



c) 90-day grace period

Figure 8-7. Kaplan-Meier survival curves for the sensitivity analysis of the discontinuation of the first gabapentinoid exposure episode

Table 8-5. Median survival time and annual survival probability of the first gabapentinoid exposure episode

	Primary analysis	Subgroup analysis		Sensitivity analysis on the grace period		
		High-dose	Non-high-dose	14 days	60 days	90 days
Median survival time (95% CI)	60 (60, 61)	360 (345, 375)	58 (58, 59)	44 (44, 45)	78 (77, 78)	79 (78, 80)
Survival probability (95% CI)						
Year 1	0.19 (0.19, 0.19)	0.50 (0.49, 0.51)	0.19 (0.18, 0.19)	0.11 (0.11, 0.12)	0.26 (0.26, 0.26)	0.26 (0.26, 0.27)
Year 2	0.13 (0.13, 0.13)	0.35 (0.34, 0.36)	0.12 (0.12, 0.12)	0.06 (0.06, 0.06)	0.19 (0.19, 0.19)	0.19 (0.19, 0.19)
Year 3	0.10 (0.09, 0.10)	0.27 (0.26, 0.27)	0.09 (0.09, 0.09)	0.04 (0.04, 0.04)	0.15 (0.15, 0.15)	0.16 (0.15, 0.16)
Year 4	0.08 (0.08, 0.08)	0.21 (0.20, 0.21)	0.07 (0.07, 0.07)	0.03 (0.03, 0.03)	0.13 (0.13, 0.13)	0.13 (0.13, 0.13)
Year 5	0.06 (0.06, 0.06)	0.16 (0.15, 0.17)	0.06 (0.06, 0.06)	0.02 (0.02, 0.02)	0.11 (0.11, 0.11)	0.11 (0.11, 0.11)

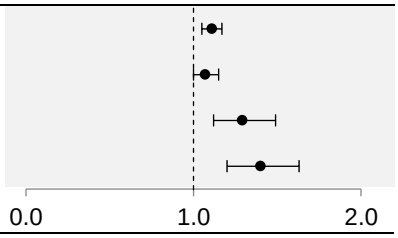
8.4.4. Association between high-dose exposure and serious adverse events

After considering the baseline demographics, baseline comorbidities, baseline pain medication use, and the effect of persistent gabaentinoid exposure, high-dose gabapentinoid exposure increases the risk of drug-related death the most out of the studied serious adverse events (aHR: 1.40, 95% CI: 1.20, 1.63). High-dose gabapentinoid exposure is associated with a significantly higher risk of suicide death (aHR: 1.29, 95% CI: 1.12, 1.49) compared to gabapentinoid users that did not have high-dose gabapentinoid exposures in the CNCP population. High-dose gabapentinoid exposure also slightly increases the risk of fracture hospitalisation (aHR: 1.11, 95% CI: 1.05, 1.17) and suicide hospitalisation (aHR: 1.07, 95% CI: 1.00, 1.15).

The adjusted baseline comorbidities and baseline pain medication uses are mostly associated with a higher risk of the serious adverse events, except baseline weak opioid use, which is associated with a significantly lower risk of the serious adverse events (Appendix 7). Baseline alcohol use problems are the strongest influential factor for fracture hospitalisaiton (aHR: 3.69, 95% CI: 3.29, 4.13) and suicide hospitalisation (aHR: 4.07, 95% CI: 3.68, 4.50), while baseline psychoactive substance misuse is the strongest influential factors for suicide death (aHR: 7.87, 95% CI: 6.60, 9.40) and drug-related death (aHR: 10.43, 95% CI: 8.70, 12.51). Persistent gabapentinoid use, as a confounding factor, is significantly associated with drug-related death (aHR: 2.38, 95% CI: 2.08, 2.73), suicide death (aHR: 2.07, 95% CI: 1.86, 2.31), suicide hospitalisation (aHR: 1.11, 95% CI: 1.08, 1.14), and fracture hospitalisation (aHR: 1.09, 95% CI: 1.07, 1.11) (Appendix 7).

Table 8-6. Association between high-dose gabapentinoid exposure and serious adverse events

	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Fracture hospitalisation	1.09 (1.01, 1.17)*	1.11 (1.05, 1.17)*	
Suicide hospitalisation	3.79 (3.54, 4.05)*	1.07 (1.00, 1.15)*	
Suicide death	4.84 (4.10, 5.71)*	1.29 (1.12, 1.49)*	
Drug-related death	6.22 (5.23, 7.40)*	1.40 (1.20, 1.63)*	



Notes: (1) HR: crude hazard ratio; aHR: adjusted hazard ratio; (2) The table presents the association between high-dose gabapentinoid exposure and the risk of serious adverse events, after adjusting for the baseline demographics, baseline comorbidities, baseline pain medication use, and the effect of persistent gabapentinoid exposure.

8.5. Discussion

Persistent gabapentinoid exposures are common in gabapentinoid users with CNCP (26.3% of episodes), while high-dose gabapentinoid exposures are comparatively rare (1.6% of episodes). Concurrent exposures with opioids (56.5%) or antidepressants (49.1%) are common in gabapentinoid users with CNCP. Compared to all gabapentinoid users with CNCP, *high-dose gabapentinoid users* tend to be younger at the age of gabapentinoid initiation, be male, be more deprived and have more baseline alcohol use problems and psychoactive substance misuse problems. Half of gabapentinoid users discontinue their first gabapentinoid exposure by day 60 after the index date, but for *high-dose gabapentinoid users* this took until day 360. High-dose gabapentinoid exposure is significantly associated with the serious adverse events in gabapentinoid users with CNCP, after considering the baseline characteristics and the effect of persistent gabapentinoid exposure.

This is the first study to investigate gabapentinoid utilisation patterns, especially persistent exposures, in patients with CNCP. A previous study reported a similarly low occurrence of high-dose pregabalin use in the general population (including patients with epilepsy) in UK primary care. Asomaning *et al.* (2016) identified 13,480 pregabalin users in the UK Health Improvement Network (THIN) primary care database in 2004-2009 and found 1.0% of the users were prescribed a higher-than-

label dose [89]. Compared to their study, which was conducted between 2004 and 2009, the 2.1% of high-dose gabapentinoid users identified from 2005-2019 in this study indicate a potential increase in the number of high-dose users over the last decade. Asomaning *et al.* (2016) also reported the median prescribed average daily dose of pregabalin for all patients as 150.0 mg/day (0.5 DDD/day) [89], which is similar to the median average daily dose (0.49 DDD/day) of gabapentinoid exposure episodes found in the CNCP population in this study. However, their dose information was reported by excluding 28.9% of the pregabalin users in the THIN database that had missing dosing information, which is prone to selection bias. In comparison, this study developed a data imputation algorithm to better estimate the average daily dose of gabapentinoid exposures.

The high-dose use of gabapentinoids in English primary care seems to be low. In a Danish drug utilisation study including 42,520 pregabalin users, 4,090 (9.6%) were treated with high-dose pregabalin (≥ 600 mg/day) for over six months, and 2,765 (6.5%) were treated with high-dose pregabalin for more than 12 months [279]. In a Swedish drug utilisation study, 8.5% of the 48,550 patients who dispensed at least 3 pregabalin prescriptions between July 2006 and December 2009 were dispensed a dose over the recommended daily dose [129]. However, these studies only studied pregabalin, included prescriptions in both primary care and secondary care, and the Swedish study had stricter inclusion criteria for pregabalin users, so no direct comparison can be made across countries.

The frequent concurrent use of gabapentinoids and opioids identified in this study is supported by a Scottish drug utilisation study using data from the Information Service Division, NHS Scotland [88]. In 2016, Torrance *et al.* (2020) identified 29,111 gabapentinoid users who filled at least one gabapentinoid prescription in Scotland and found that 49.9% were co-prescribed opioids and 26.8% were co-

prescribed benzodiazepines [88]. Since Torrance *et al.* (2020) defined a co-prescription as any opioid or benzodiazepine prescribed in the same year as gabapentinoids, it is likely to show a higher co-prescribing rate than the concurrent exposure rate in this study, which strictly requires overlap between exposures. Therefore, the 15.9% concurrent benzodiazepine use among gabapentinoid users found in this study is comparable to their result. However, the result of 56.5% concurrent opioid use among gabapentinoid users in this study (vs. 49.9% co-prescribed opioids in their study) suggests concurrent exposure to gabapentinoids and opioids is either more common in patients with CNCP compared to the general population, or more common in England compared to Scotland.

There is no previous drug utilisation study evaluating persistent gabapentinoid exposures. The results of this study suggest that the majority of gabapentinoid prescriptions in English primary care have around 28 days of supply, which are likely to be repeat prescriptions following the NHS 28-day repeat prescribing policy [276]. However, although each individual prescription has 28 days of supply, these prescriptions could be continuous and add up to persistent gabapentinoid exposures that last over 6 months for 26.3% of gabapentinoid exposures and over 12 months for 15.3% of gabapentinoid exposures.

The discontinuation of the first gabapentinoid exposure episode was first evaluated in this study, although a German cross-sectional study provided some supporting evidence. Viniol *et al.* (2019) identified gabapentinoid users with a pain diagnosis in 2013 from a German health insurance database, then checked for further gabapentinoid prescriptions in the following two consecutive quarters and again at year 2 of the follow-up period for these users [280]. If a gabapentinoid user did not receive a gabapentinoid prescription in the next two quarters or at year 2 of the follow-up, a discontinuation is detected. Their study found 85% of the identified

users discontinued gabapentinoid treatment [280], which is similar to the survival probability of 87% for the first gabapentinoid exposure at year 2 after the index date in this study. However, their cross-sectional study did not account for loss of follow-up and did not follow the patients continuously, so cannot provide an unbiased estimation of discontinuation over time like this study.

Although persistent gabapentinoid use was found to be common in patients with CNCP in the gabapentinoid utilisation pattern analysis and the drug survival analysis in this study, the efficacy and safety of persistent (i.e. long-term) gabapentinoid use for chronic pain has not been evaluated. The randomised controlled trials (RCTs) assessing the pain relief outcomes of gabapentinoids typically have a 12-week follow-up period [79-82], which does not provide evidence for gabapentinoids' long-term pain relief efficacy. The National Institute for Health and Care Excellence (NICE) pharmacological management guideline for neuropathic pain recommended gabapentinoids as first-line therapy for neuropathic pain in the UK, but no time frame for the gabapentinoid treatment was suggested in the guideline [44].

Similarly, the risk of persistent gabapentinoid use for chronic pain has also not been evaluated in epidemiological studies. In the follow-up trial of an RCT investigating gabapentin's efficacy for treating partial seizures in 1994, 240 patients continued gabapentin therapy (maximum dose 2400 mg/day) for up to 120 weeks and reported no significant increase in the number or intensity of side effects [281]. However, a recent case report review article pointed out that the long-term tolerance of gabapentinoids, especially pregabalin, might lead to drug dependence [282]. Therefore, it is possible that persistent gabapentinoid exposure is relatively safe if the patient is on a stable dose and shows no signs of drug dependence, but further

studies are still warranted to evaluate the efficacy and safety of persistent gabapentinoid use.

In the subgroup analysis of the discontinuation of the first gabapentinoid exposure episode, *high-dose gabapentinoid users* tend to continue their first gabapentinoid exposure significantly longer than *non-high-dose gabapentinoid users*. This finding supports the hypothesis that high-dose gabapentinoid use is likely to build up from persistent use. However, the pharmacological and psychological mechanism between persistent and high-dose gabapentinoid use should be further investigated to support this hypothesis [283].

Published studies have found similar dose-dependent associations between high-dose gabapentinoid exposure and the risks of the serious adverse events in different populations to this study. Rentsch *et al.* (2020) conducted a cohort study including 431,920 gabapentin users and their matched non-users between 2002 and 2015 from the US Department of Veterans Affairs National Corporate Data Warehouse. They investigate the associations between gabapentin and falls and fractures and gabapentin and altered mental status [101]. They found a dose-dependent risk of fracture or fall associated with gabapentin exposure (aRR: 1.23, 95% CI: 1.13, 1.34 for <600 mg gabapentin compared to to aRR: 1.90, 95% CI: 1.50, 2.40 for >=2,400 mg gabapentin), but not for altered mental status [101]. However, Rentsch *et al.* (2020) measured the pregabalin dose at the initiation of the two-year follow-up period, which does not account for potential dose changes during the follow-up period. In contrast, high-dose gabapentinoid exposure was considered as a time-varying covariate in this study, which models the real situation better.

A self-controlled study using a Swedish national prescribing database during 2006-2013 found that the risk of suicide for high gabapentinoid doses over 2 DDDs/day

(aHR: 1.38, 95% CI: 1.27, 1.50) was higher than that for moderate gabapentinoid doses of 1-2DDDs/day (aHR: 1.31, 95% CI: 1.22, 1.40), though the difference between these is not statistically significant [20]. The non-significance is probabaly due to a small sample size of high-dose gabapentinoid exposures. No previous epidemiological study has investigated the dose-dependent association between gabapentinoids and drug-related death. However, since post-mortem studies frequently report cases of gabapentinoid poisoning, high-dose gabapentinoid exposure is likely to be a risk factor for drug-related death [104, 105].

This study used a large primary care electronic health record that provides rich information on prescriptions, which enabled the analysis of the gabapentinoid utilisation patterns. A data cleaning and imputation process was developed to deal with missing information in the prescription data, which avoids the selection bias that would be introduced by simply excluding prescriptions with missing information. The concurrent exposures of gabapentinoids with other pain medications were measured using overlap time windows , which account for the differences in common treatment times between the pain medications. This study used a drug survival analysis to estimate the discontinuation of the first gabapentinoid exposure episode, which is a recently adopted use of this technique in the field of drug utilisation research [284]. A sensitivity analysis was applied in the drug survival analysis to test for the potential influence of the grace period length. This study applied a Cox proportional hazard model with gabapentinoid utilisation patterns set as time-varying covariates to assess the association between high-dose gabapentinoid exposure and serious adverse events, so changes of high-dose gabapentinoid exposure status over the follow up period are accounted for in the analysis.

There are several limitations of this study. Firstly, the drug utilisation measure in this study have many assumptions which may not always hold. For example, this study assumed that prescriptions recorded in the GP system are dispensed and taken by the patients, but patients with chronic pain tend to have low adherence rates to medication [272]. A grace period was applied to measure the length of gabapentionid exposure episodes to mitigate this assumption being violated, but violations can still occur, depending on patient behaviour. Secondly, the prevalence of gabapentinoid utilisation patterns was not available in this study because the annual total number of patients diagnosed with CNCP is not available from the CPRD, due to its data extraction process. Thirdly, the utilisation patterns identified in this study are limited to patients with CNCP and may not be generalisable to other populations. Fourthly, a single set of confounding factors were adjusted in the Cox proportional hazard model for four different serious adverse events, which may not fully adjust the confounding effect for each serious adverse event.

In conclusion, this study provided an overview of gabapentinoid utilisation patterns in patients with CNCP in English primary care. Persistent gabapentinoid exposure is common in gabapentinoid users, while high-dose use is rare. High-dose gabapentinoid users tend to remain on the first gabapentinoid exposure episode for much longer than non-high-dose users. High-dose gabapentinoid exposure was found to be significantly associated with the risk of serious adverse events in gabapentinoid users with CNCP. Further studies can investigate the association between other gabapentinoid utilisation patterns and safety issues, and account for the time-to-onset of the adverse events.

Chapter 9. The risk of fracture hospitalisation in gabapentinoid exposure periods in patients with chronic non-cancer pain in English primary care

9.1. Introduction

Dizziness is one of the most common side effects of gabapentinoids and often occurs at the beginning of gabapentinoid treatment [8]. It can cause patients to fall and suffer consequential events such as fracture hospitalisation. In Chapter 7, gabapentinoid users were found to have a higher risk of fracture hospitalisation compared to non-users in the CNCP population. However, the risk of fracture during a gabapentinoid exposure may vary depending on the time since the beginning of the exposure.

Mukai *et al.* (2019) identified over 8 million pregabalin-related adverse event reports in US Food and Drug Administration Adverse Event Reporting System database and the Japanese Adverse Drug Event Report database from 2004-2016 [230]. They generated a time-to-onset profile of adverse events related to falls (AEFs) (i.e. adverse events that would cause falls such as somnolence, dizziness, loss of consciousness, etc.) and found the majority of the pregabalin AEFs occurred within 1 week after the initiation of pregabalin [230]. This study indicates a short-term risk of fracture after pregabalin exposure, which is likely to also exist in gabapentin because of the similar pharmacological mechanism of gabapentin on the central nervous system. Therefore, the risk of falls and fractures is hypothesised to be higher in the period shortly after the initiation of gabapentinoids compared to later time periods, because patients may become tolerant and can manage dizziness and other CNS-related side effects after exposure to gabapentinoids for extended periods [112].

In order to study the risk of fracture hospitalisations in different time periods of a gabapentinoid exposure, time-varying factors that are relevant to fracture risk need adjusting. Age is one of the strongest time-varying influential factors that influence the risk of fracture hospitalisation over time [285]. Season is another time-varying influential factor. A study using the UK National Hip Fracture Database analysed almost all hip fractures that happened in patients over 60 years in the UK and found an 8% increase in hip fractures in winter months (December to February) than in summer months (June to August) in the study period between April 2011 and March 2018 [286].

In addition to age and season, diseases and drug exposures are also time-varying factors that influence the risk of fracture. Osteoporosis and rheumatoid arthritis are diseases that have direct mechanical links with fractures and could be newly diagnosed during the observation period. The occurrence of osteoporosis is characterised by low bone mineral density and therefore has a direct impact on fracture risk [264]. Similarly, rheumatoid arthritis (RA) is associated with a higher fracture risk because the inflammation process and the therapy drug (such as oral glucocorticoids) can both lead to bone loss [265]. Among the common drugs that could be used by gabapentinoid users with chronic non-cancer pain (CNCP), opioids [214], benzodiazepines [287], antidepressants [288], and Z-drugs [287] have been found to be associated with an increased risk of fracture, either due to their acute impact on the CNS or their anticholinergic and sedating effects.

9.2. Aim and objectives

This hypothesis-testing study aims to investigate the risk of fracture hospitalisation for different time periods during gabapentinoid exposures. The objectives of this study are:

(1) To estimate the risk of fracture hospitalisation for the different time periods of gabapentinoid exposures, compared to non-use baseline periods in patients with CNCP.
(2) To assess the fracture hospitalisation risk for different time periods of gabapentinoid exposures for gabapentin-only and pregabalin-only users and for male and female patients in patients with CNCP.

9.3. Methods

9.3.1. Study design and data sources

This Self-Controlled Case-Series (SCCS) study used primary care data from CPRD GOLD and Aurum, and linked to HES APC between 1 January 2005 and 31 December 2019. The gabapentinoid users with CNCP and their baseline characteristics were obtained from CPRD primary care data. Fracture hospitalisations were identified from the HES APC database.

Fracture is a complicated health outcome that has many measurable and unmeasurable influential factors which are not easily accounted for in traditional epidemiological study designs, but can be adjusted for in a self-controlled study design where patients act as their own control. In a self-controlled study, characteristics that remain constant over the observation periods (such as gender, ethnicity, genes, socioeconomic status, etc.) are cancelled out [289].

There are two self-controlled study designs: SCCS and self-controlled case cross-over studies [290]. A self-controlled case cross-over study is more similar to a case-control study because it anchors at the date of the event. From the event, it traces back for the occurrence of exposures in fixed time frames and compares them using odds ratios to a baseline time frame [291]. In contrast, the SCCS study design is

more similar to a cohort study because it anchors at the date when an exposure is initiated. It traces forward from the first day of each exposure to look for events in the following time periods and compares them using an incidence rate ratio to baseline time periods with no exposure [289]. Since this study focuses on the risk of fracture hospitalisation during gabapentinoid exposure, rather than the fraction of fracture hospitalisations that are preceded by gabapentinoid exposures, SCCS is more appropriate for this study.

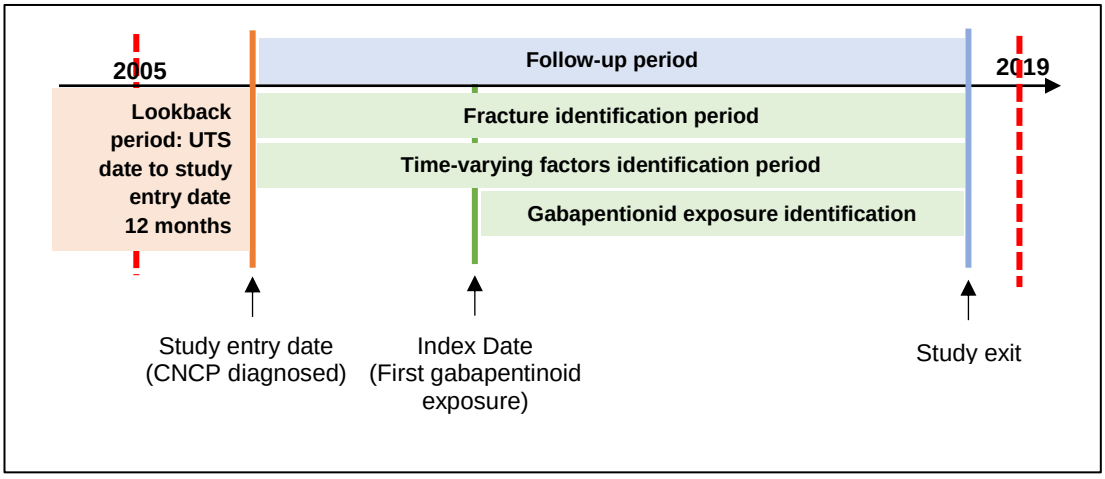


Figure 9-1. Definition of the follow-up time for the self-controlled case-series study

A patient's follow-up period is defined as the period from the study entry date to the study exit date (Figure 9-1). The SCCS study divides the follow-up period into a series of smaller periods. These divisions are added each time a study-relevant covariate changes (e.g. dates when drug exposure periods begin or end, when the season changes, when the patient age changes, etc.).

9.3.2. Study population

Adult gabapentinoid users with CNCP that had at least one fracture hospitalisation during the follow-up period were identified as the *study cohort*.

The identification process of the *gabapentinoid user* cohort in the CNCP population from the CPRD primary care databases was described in Chapter 6. Fracture hospitalisations among the *gabapentinoid user* cohort were identified using ICD-10 codes from the HES APC database "primary diagnoses across a hospitalisation" sub-dataset. Fracture hospitalisations with missing event dates were excluded because they were assumed to be invalid. Fractures that had another fracture diagnosis at the same site (i.e. having the same ICD-10 code in the HES APC database) in the 14 days before were excluded because they were assumed to be a repeat record of the previous fracture. This is because a single event can be repeatedly recorded if a patient is seen by more than one consultant during a hospital stay. The follow-up period for each individual patient to observe fracture hospitalisations, gabapentinoid exposures, and other confounding factors starts from the study entry date when the patient was first diagnosed with CNCP and ends on the study exit date as mentioned in Section 5.5.1, Chapter 5 (Figure 9-1).

The *study cohort* was categorised into two sets of subgroups for further analyses: (1) gabapentin-only users and pregabalin-only users; (2) male and female gabapentinoid users.

The gabapentin-only and pregabalin-only user subgroups are defined as patients in the *study cohort* who were only prescribed either gabapentin or pregabalin during the follow-up period. Patients that were prescribed both gabapentin and pregabalin during the follow-up period are excluded from the subgroups. This is to avoid complications in separating the effects of chronologically close or overlapping gabapentin and pregabalin exposures. The *study cohort* was divided into male and female subgroups to evaluate the effect of gender on fracture risk.

9.3.3. Exposure periods

The follow-up period was divided into exposure periods and non-exposure periods depending on whether the period included exposure to gabapentinoids (Figure 9-2). As defined in Chapter 8, a gabapentinoid exposure episode consists of consecutive prescriptions with less than a 30-day gap between them, assuming patients are under gabapentinoid exposure during the gap (Section 8.3.3). The exposure period starts at the date of the first prescription in the episode and ends on the last day covered by gabapentinoid prescriptions in the episode. This assumes patients start taking gabapentinoids as soon as they are prescribed.

To observe any changes in risk over the exposure period, each exposure period was divided into four risk periods, counting from day one of the exposure period: 1-7 days, 8-14 days, 15-28 days, and 29+ days. If the number of days covered by the exposure period does not cover all four risk periods, then only the risk periods that were covered were applied (Figure 9-3).

Gabapentinoid exposure periods were assumed to be independent in this study, meaning that patients have the same tolerance to the dizziness side effect for the first and all subsequent exposure periods. However, a sensitivity analysis was conducted to check this assumption by separating each patient's first gabapentinoid exposure period from all the subsequent exposure periods during the follow-up time of that patient. Both the first and subsequent gabapentinoid exposure periods were split into the same risk periods: 1-7 days, 8-14 days, 15-28 days, and 29+ days.

Similarly, gabapentinoid exposure periods were assumed to have no dose-dependent effect on fracture hospitalisation risk in this study. A sensitivity analysis was conducted to check this assumption by separating high-dose gabapentinoid

exposure periods from the rest of the gabapentinoid exposure periods to test for the potentially higher risk of fracture hospitalisation in high-dose gabapentinoid exposure periods. Both the high-dose and non-high-dose exposure periods were split into the four risk periods.

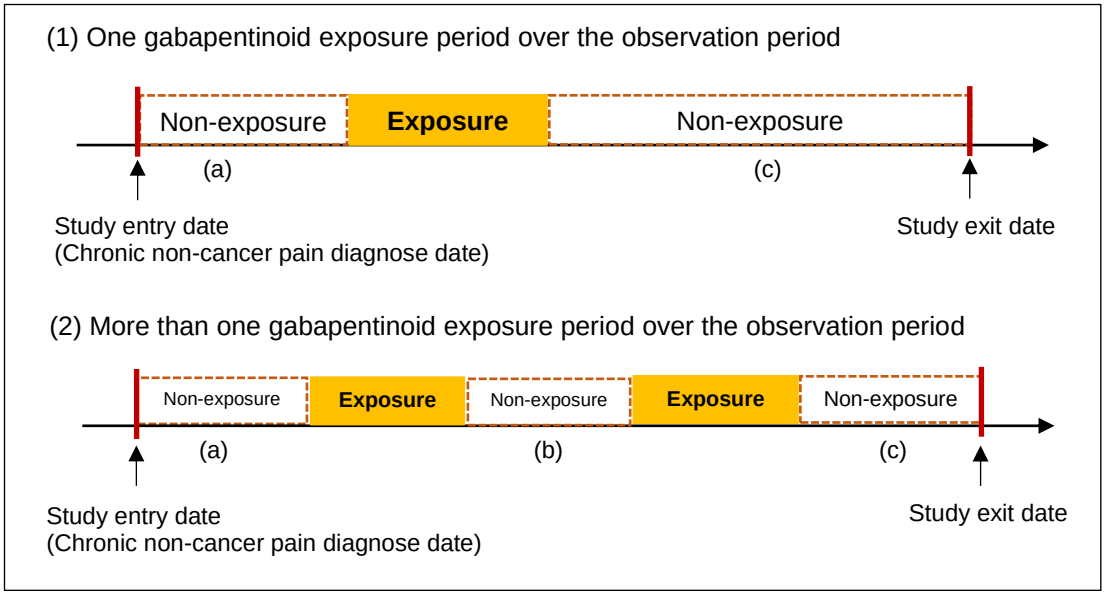


Figure 9-2. Example cases for illustrating gabapentinoid exposure and non-exposure periods

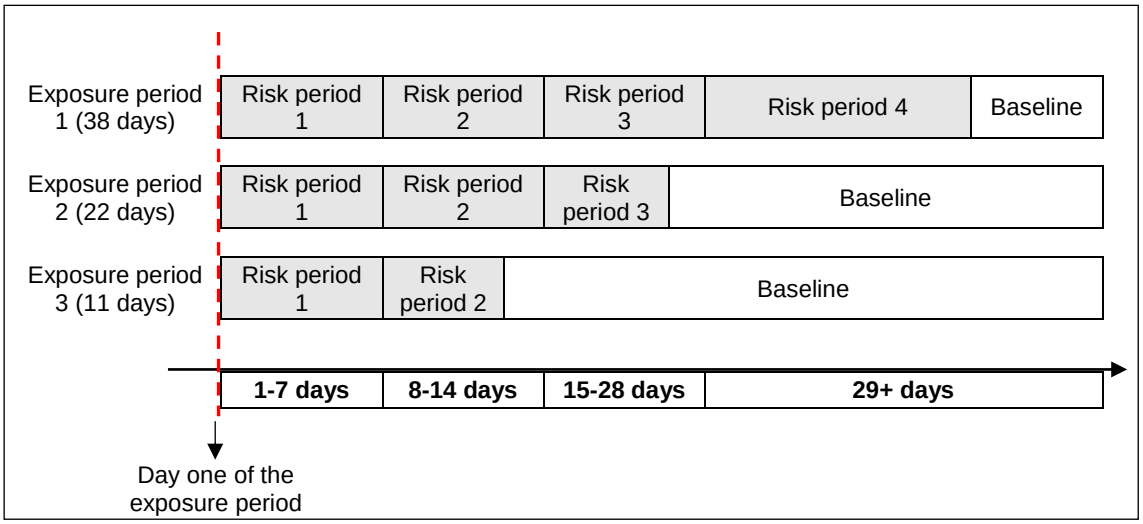


Figure 9-3. Example cases for illustrating the time periods during a gabapentinoid exposure

Note: Exposure period 1 covers 38 days, so the end of this episode falls into the fourth risk period (29+ days). Exposure period 2 covers 22 days, so the end of this exposure period falls into the third risk period (15-28 days), so exposure period 2 only has three risk periods:

1-7 days, 8-14 days and 15-28 days. Similarly, Exposure period 3 covers 11 days, so does not have the third (15-28 days) and fourth (29+ days) risk periods.

9.3.4. Non-exposure periods

Gabapentinoid non-exposure periods are defined as time in the follow-up period that was not covered by gabapentinoid exposure periods, including the period (a) from the study entry date to the index date of gabapentinoids; (b) from the day after an exposure period to the day before the next exposure period (if there are >1 gabapentinoid exposure periods for that patient); or (c) from the day after the last exposure period to the study exit date (Figure 9-2).

The SCCS study design aims to compare incidence rates of the outcome event between exposure periods and baseline periods, but the incidence rates in the non-exposure periods could be affected by the exposure, violating the SCCS key assumption that subsequent exposures should not be affected by previous events [292]. Modifications to the SCCS design, such as introducing pre-exposure or post-exposure periods, can be applied to mitigate this potential violation of the model assumptions [289].

In this study, one potential violation of the model assumptions is gabapentinoids being prescribed for acute pain after a fracture hospitalisation, which would increase the fracture hospitalisation risk in the period immediately before the exposure. This bias could be mitigated by dividing the non-exposure periods into separate pre-exposure periods and baseline periods, and then comparing the incidence rates of the outcome between the exposure periods and the baseline periods. Another potential violation could be gabapentinoid residue in the body maintaining its effect for a period of time after the last day of the exposure period, which could alter the incidence of fracture hospitalisation for a short time after the exposure period ends.

However, since the half-life of gabapentinoids is approximately 6 hours [7], the residual effect of gabapentinoid exposure is assumed to be negligible. Therefore, a post-exposure period to mitigate bias caused by residual effects was not introduced in this study.

Pre-exposure period

A pre-exposure period is defined as a short time period before the exposure period, during which the risk of adverse events may be related to the following exposure. An exposure caused by a previous event is defined as an event-dependent exposure. Pre-exposure periods should be excluded from the baseline period if event-dependent gabapentinoid exposure could occur during the pre-exposure period, otherwise it will bias the baseline risk of fracture hospitalisation.

A pre-exposure period was applied in the sensitivity analysis for this study because event-dependent gabapentinoid exposures are likely to occur, according to the histogram of the closest fracture hospitalisations near the first day of gabapentinoid exposures (Figure 9-4). The 90 days before a gabapentinoid exposure period have the highest frequency of fracture hospitalisation, indicating a potential for event-dependent exposure in the pre-exposure period. However, since gabapentinoids are not indicated for acute pain (including fracture acute pain) and no evidence has shown them to be commonly used in treating fracture pain, the pre-exposure period was only included in sensitivity analyses to test the robustness of the primary analysis.

Two lengths of pre-exposure period were tested in the sensitivity analyses. A 28-day pre-exposure period was chosen based on the assumption that acute pain from fracture hospitalisations could cause the prescribing of gabapentinoids, which

theoretically should occur a short time after the fracture hospitalisation. A 90-day pre-exposure period was chosen as it was informed by the distribution of the nearest fracture hospitalisations close to the start of gabapentinoid exposures (Figure 9-4). Although a large timescale causal link of fracture causing gabapentinoid exposure cannot be mechanically justified (i.e. the reasons why gabapentinoids are prescribed in the 90 days after a fracture hospitalisation), this was tested to investigate the unexpected significant protecting effect seen in the 29+ days risk period. In a scenario where two gabapentinoid exposure periods occur within 90 days of each other, the exposure periods are unchanged, but the pre-exposure period is truncated to not overlap with the first exposure period.

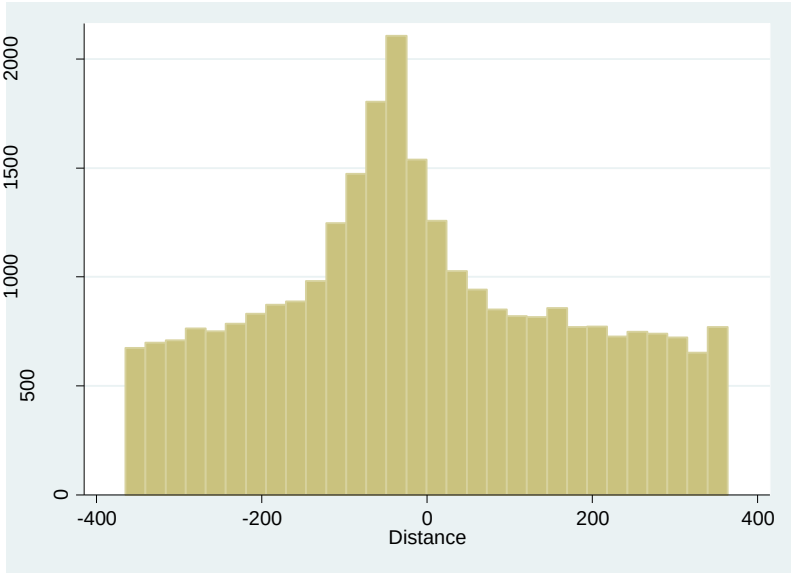


Figure 9-4. Distribution of the time to the nearest fracture hospitalisation from day one of the gabapentinoid exposure period

Note: the bin width is 30 days

Baseline period

A baseline period is defined as a non-exposure period, excluding pre-exposure periods. In the primary analysis where pre-exposure periods were not considered, all non-exposure periods were defined as baseline periods. In the sensitivity

analysis that introduced pre-exposure periods, pre-exposure periods were excluded from the non-exposure periods to form the baseline periods (Figure 9-5).

9.3.5. Time-varying covariates

The SCCS design uses patients as their own control, so the effect of influential factors that remain constant over the follow-up period is cancelled out [292]. However, influential factors that can change during the follow-up period are not adjusted for naturally in the SCCS study design, and are therefore defined as time-varying factors that need adjustment in the analysis. In this study; age, season, diagnosis of osteoporosis and rheumatoid arthritis, and exposures to immediate fracture-related drugs (opioids, antidepressants, benzodiazepines, and Z-drugs) were identified as time-varying factors in the SCCS analysis (Figure 9-5). Their associations with fracture are described in the introduction section (Section 9.1).

Osteoporosis, rheumatoid arthritis, and fracture-related drug exposure were treated as binary covariates in the SCCS analysis; valued as either 0 or 1 (Figure 9-5). Age and season were measured as categorical covariates in the SCCS analysis. The follow-up time periods were assigned corresponding values for the age group and season each time the patients' age group or season changed during the follow-up time (Figure 9-5).

Osteoporosis and rheumatoid arthritis diagnoses were identified throughout the observation period using the code lists generated in Chapter 5 from CPRD GOLD clinical files and Aurum observation files. Any missing event dates for diagnoses were imputed using the record entry date (the date when the event was entered into the practice system). Since osteoporosis and rheumatoid arthritis are non-reversible diseases, all time periods after the first identified diagnosis categorised the disease

as being present, and were valued as 1. For example, if a patient was diagnosed with osteoporosis during the follow-up period, all time periods from the study entry date to just before the diagnosis are valued as 0, and any time periods from the diagnosis to the study exit date are valued as 1 (for the osteoporosis covariate).

Osteoporosis is often underdiagnosed due to presenting limited symptoms that could allow early diagnosis [293], so the real onset date of osteoporosis often precedes diagnosis by a significant time. However, fracture events often motivate bone mass tests that diagnose osteoporosis [293]. Thus, some fractures that occurred while the patient had osteoporosis can often precede diagnosis, causing a peak in the number of diagnoses of osteoporosis after fracture events. This increases the estimated fracture risk in the osteoporosis-free period, and biases the association between osteoporosis and fracture. Therefore, the diagnosis of osteoporosis recorded in the CPRD was moved 1 year earlier in one sensitivity analysis to adjust for this bias, assuming that the patient had osteoporosis for at least 1 year before diagnosis. This removes the bias by moving the diagnosis to before the fracture event.

Prescriptions of the fracture-related drugs including opioids, antidepressants, benzodiazepines, and Z-drugs during the follow-up period were identified using the product codes identified in Chapter 5 from CPRD GOLD therapy files and Aurum drug issue files. The selected fracture-related drugs are assumed to have a similar probability of causing fracture hospitalisations because no substantial difference was observed between them (aHR range: 1.03-1.55) in Chapter 7 for fracture hospitalisation. Therefore, they were treated as one time-varying factor (i.e. the fracture-related drug exposure covariate). The identification of a fracture-related drug exposure episode was similar to the gabapentinoid exposure episode identification process, where consecutive prescriptions with less than a 30-day gap

were defined as one exposure episode. However, unlike for gabapentinoids, the length of each individual prescription was not calculated using an algorithm, but instead all prescriptions were assumed to cover 28 days. This simplification was made due to the large amount of time that would be required to develop the algorithms to define the prescription period for each drug category. Time periods covered by an exposure episode were valued as 1, and were otherwise valued as 0 (for the fracture-related drug covariate).

Age was treated as a categorical variable of 1-year age groups. Since the age of patients in the CPRD is recorded by birth year only, the date of age increase was set as the 1st of January each year for all patients. The seasons were defined as spring (March to May), summer (June to August), autumn (September to November) and winter (December to February). Winter was set as the reference group in the SCCS analysis (i.e. denoted as 0).

(a) Gabapentinoid exposure periods

No pre-exposure	Baseline (0)		1-7 (1)	8-14 (2)	15-28 (3)	>28 (4)	Baseline (0)
With pre-exposure	Baseline (0)	Pre-exposure (1)	1-7 (2)	8-14 (3)	15-28 (4)	>28 (5)	Baseline (0)

(b) Time-varying factors

Age	Age group 71 (71)					
Season	Winter (0)			Spring (1)		
Osteoporosis	Not diagnosed (0)					
Rheumatoid arthritis	Not diagnosed (0)				Diagnosed (1)	
FRD exposure	Not exposed (0)		Exposed (1)			Not exposed (1)
Follow-up time	→					

Figure 9-5. An example case to illustrate the value assignment of gabapentinoid exposure periods and time-varying covariates

Note: 1. Numbers in brackets are the value assigned to the corresponding covariates as labelled on the left.
2. Above is a short follow-up period of an example patient aged 71 at the 35-day gabapentinoid exposure. The gabapentinoid exposure period is categorised into 1-7 days, 8-14 days, 15-28 days and 29+ days. The non-exposure periods are all defined as baseline period in the design without pre-exposure analysis (i.e. primary analysis, "no pre-exposure" in the figure). A 14-day or 28-day pre-exposure period is separated from baseline in the design with pre-exposure period (i.e. sensitivity analyses, "with pre-exposure" in the figure). The patient was aged 71 in the above observation period and therefore the age covariate remained 71 for the above follow-up period. The season in the above time period changed and therefore the value for season covariate changed from 0 indicating winter to 1 indicating spring the time period. The patient was not diagnosed with osteoporosis over this time period, so was allocated 0 for the osteoporosis covariate. The patient was diagnosed with rheumatoid arthritis over this time period, so the value for rheumatoid arthritis covariate was changed from 0 to 1 and stayed at 1 for the rest of the study period.
3. FRD: fracture-related drugs

9.3.6. Analytical methods

Descriptive statistics were applied to the characteristics of patients and fracture hospitalisations. Patients' gender, disease diagnosis, and fracture frequency by patient or season were reported as numbers and proportions. The mean and standard deviation (SD) were reported for age at the study entry date and the follow-up time was measured in years. Median and interquartile range (IQR) was reported for the Index of Multiple Deprivation (IMD) deciles.

A fixed-effect Poisson regression with an absorbing function was applied to estimate the incidence rate ratios (IRRs), which are the ratio of the risk of fracture hospitalisation in the gabapentinoid exposure periods compared to non-exposure baseline periods [292]. The absorbing function makes the model fitting more efficient compared to models without an absorbing function, because the absorbing function does not estimate individual-specific random effects [294]. The details of the SCCS analysis are described in Appendix 6. Crude IRRs were generated by fitting covariates individually into the fixed-effect Poisson model. Adjusted IRRs (aIRRs) were generated by fitting relevant covariates into the fixed-effect Poisson together. The crude IRRs and adjusted IRRs were reported with 95% confidence intervals (95% CIs). The aIRRs for each model were also presented in forest plots.

A likelihood ratio test (Bayesian information criterion, BIC) was applied to select covariates to identify the best-fitting fixed-effect Poisson regression model. Likelihood ratio tests are normally used to test the fitting of two nested models (i.e. one model is a special case of the other model), where the null hypothesis is that the simpler model fits better [295].

Two subgroup analyses were conducted to study the aIRR difference between (1) gabapentin and pregabalin and (2) between males and females. The purpose of these subgroup analyses is to investigate if the fracture hospitalisation risk associated with gabapentinoid exposure is different for different gabapentinoid drugs and genders.

Six sensitivity analyses were conducted to test the robustness of the SCCS results.

(1) A 28-day pre-exposure period was applied to adjust for the potential event-dependent gabapentinoid exposure that would violate the assumptions of SCCS;
(2) A 90-day pre-exposure period was applied to adjust for the potential event-dependent gabapentinoid exposure that would violate the assumptions of SCCS;
(3) The first gabapentinoid exposure period was separated from the following gabapentinoid exposure periods to test for the potential of better tolerance during the following exposures;
(4) The high-dose gabapentinoid exposure periods were separated from the non-high-dose gabapentinoid exposure periods to test for the potential dose-dependent risk of fracture hospitalisation following gabapentinoid exposures;
(5) The diagnosis date of osteoporosis was moved 1 year earlier to adjust for potential delay in osteoporosis diagnosis;
(6) Only the first fracture for each patient was included to remove the potential non-random occurrence of the following recurrent fractures, as the existence of later fractures could be dependent on previous fractures.

All data cleaning and analyse processes were conducted using STATA C14 (StataCorp, 2021, Texas, USA).

9.4. Results

9.4.1. Cohort selection and baseline characteristics

The study cohort consists of 40,743 gabapentinoid users identified from the CNCP population that had at least one fracture hospitalisation during the follow-up period, with a total of 49,678 fracture hospitalisations identified (Figure 9-6). During the follow-up period, 32.0% (n=13,023) of the study population were diagnosed with osteoporosis, and 4.1% (n=1,654) were diagnosed with rheumatoid arthritis (Table 9-1). Almost all of the study cohort (98.4%) was exposed to at least one fracture-related drug during the observation period.

In the study cohort, 33,879 (83.2%) patients had only one fracture hospitalisation, 5,379 (13.2%) had two fracture hospitalisations, and 103 (0.3%) patients had five or more fracture hospitalisations during the follow-up time (Table 9-1). A slightly higher proportion of fracture hospitalisations occurred in summer, but the percentage changed only a small amount between seasons (Table 9-1).

Two sets of subgroups were selected for further analyses. Among the 40,743 patients identified in the study cohort, the 27,955 (68.6%) females were selected as the female subgroup, and the 12,788 (31.3%) males were selected as the male subgroup. There were 22,999 (56.4%) gabapentin-only users and 9,955 (24.4%) pregabalin-only users identified from the study cohort.

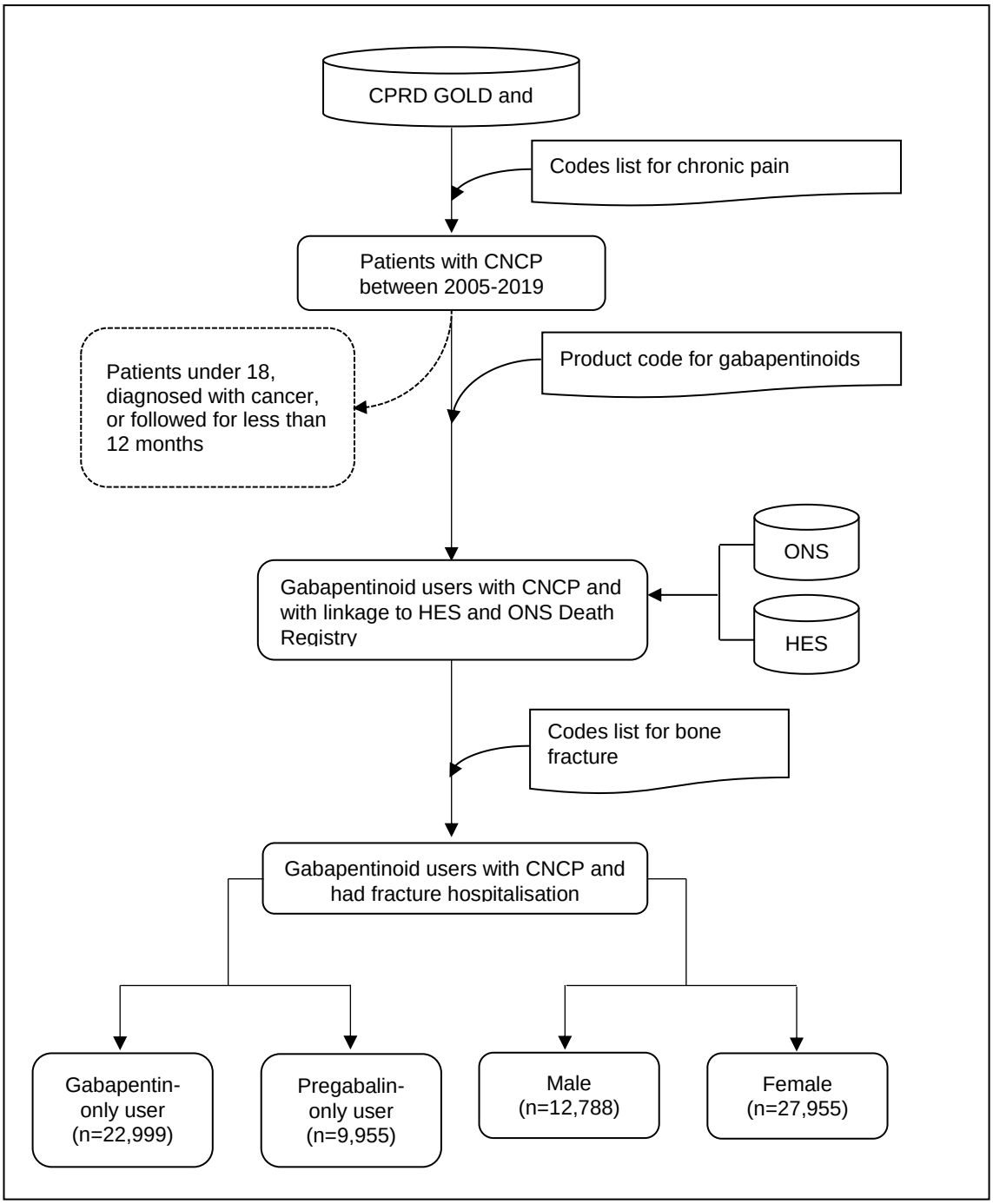


Figure 9-6. Flow chart for generating the study cohorts and sub-cohorts

Note: CPRD, Clinical Practice Research Datalink; CNCP, chronic non-cancer pain; ONS, Office for National Statistics; HES, Hospital Episode Statistics

Table 9-1. Descriptive statistics for gabapentinoid users with fracture hospitalisation

	Gabapentinoid users
Total number of patients	40,743
Demographics	
Mean age at study entry date in years (SD)	60.08 (16.99)
Number of female patients (%)	27,995 (68.7%)
Mean follow-up time in years (SD)	9.92 (3.80)
Time-varying factors	
Patients with osteoporosis (%)	13,023 (32.0%)
Patients with rheumatoid arthritis (%)	1,654 (4.1%)
Patients with exposure to fracture-related drugs (%)	40,103 (98.4%)
Number of fracture hospitalisations in patients	
Patients with 1 fracture hospitalisation (%)	33,879 (83.2%)
Patients with 2 fracture hospitalisations (%)	5,379 (13.2%)
Patients with 3 fracture hospitalisations (%)	1,106 (2.7%)
Patients with 4 fracture hospitalisations (%)	276 (0.7%)
Patients with 5 or more fracture hospitalisations (%)	103 (0.3%)
Number of fracture hospitalisations by season	
Spring (%)	12,329 (24.82%)
Summer (%)	12,788 (25.74%)
Autumn (%)	12,281 (24.72%)
Winter (%)	12,280 (24.72%)

9.4.2. Risk of fracture hospitalisation in gabapentinoid exposure periods

Primary analysis

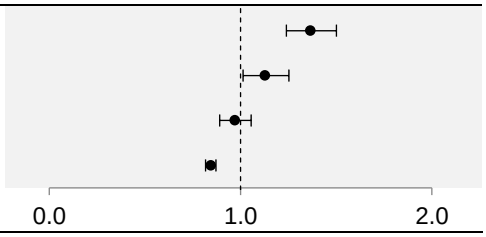
Compared with the baseline non-exposure periods, the risk of fracture hospitalisation is higher during gabapentinoid exposure periods, and the risk is highest at the start of each exposure period. Considering all adjusted covariates, the gabapentinoid risk periods of 1-7 days (aIRR: 1.36, 95%CI: 1.24, 1.50) and 8-14 days (aIRR: 1.13, 95%CI: 1.01, 1.25) showed a significantly higher risk of fracture hospitalisation compared to the baseline non-exposure periods (Table 9-2). Later in each exposure period, the risk falls, becoming insignificant for the risk period of 15-

28 days, and falling to a significantly lower risk in the 29+ days risk period (aIRR: 0.84, 95%CI: 0.82, 0.87) (Table 9-2).

In addition to gabapentinoid exposure periods, some of the adjusted covariates in the SCCS analysis also showed a significant effect on the risk of fracture hospitalisation (Appendix 8). The risk of fracture hospitalisation increases with age. Time periods with rheumatoid arthritis have a significantly higher risk of fracture hospitalisation compared to periods free from rheumatoid arthritis (aIRR: 1.27, 95% CI: 1.13, 1.43). One suspicious covariate result was for osteoporosis, which showed a lower risk of fracture hospitalisation in periods with osteoporosis compared to periods free from osteoporosis (aIRR: 0.67, 95%CI: 0.64, 0.70), but this was explained later in a sensitivity analysis (Section 9.4.3). The season was not significantly associated with the risk of fracture hospitalisation but was still included in the model as suggested by the likelihood ratio test (Appendix 8).

Table 9-2. SCCS results for the primary analysis on the risk of fracture hospitalisation for risk periods of gabapentinoid exposure periods

Risk Periods	IRR	aIRR	aIRR
1-7 days	1.64 (1.49, 1.80)*	1.36 (1.24, 1.50)*	
8-14 days	1.35 (1.22, 1.50)*	1.13 (1.01, 1.25)*	
15-28 days	1.17 (1.07, 1.27)*	0.97 (0.89, 1.06)	
29+ days	1.17 (1.14, 1.21)*	0.84 (0.82, 0.87)*	



*Note: (1) * indicates a P-value lower than 0.05; (2) The table presents the association between gabapentinoid exposure risk periods and fracture hospitalisation (reference group: baseline gabapentinoid non-exposure period), after adjusting for age, season, diagnosis of osteoporosis, diagnosis of rheumatoid arthritis, exposure to fracture-related drugs.*

Subgroup analyses

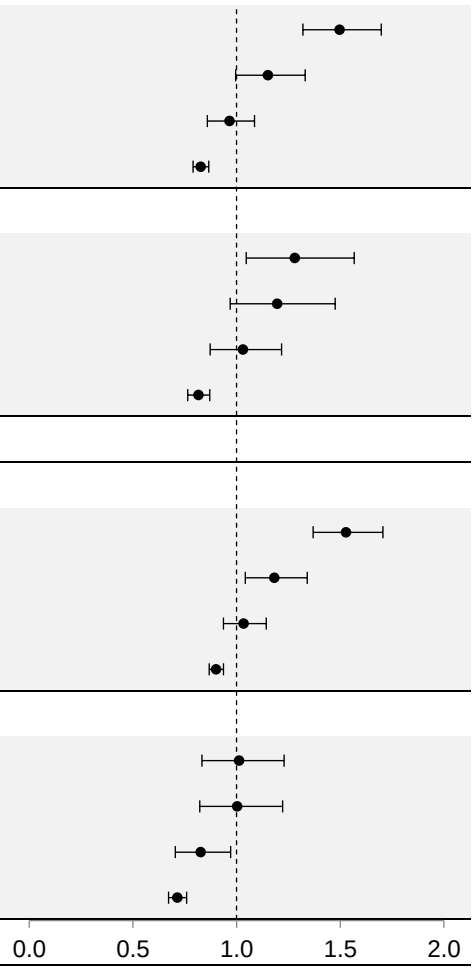
The risk of fracture hospitalisation during exposure periods showed similar trends when gabapentinoid exposures were divided into gabapentin-only and pregabalin-

only, with the highest risk occurring 1-7 days from the start of the exposure, and lower risk in the following risk periods (Table 9-3). The fracture hospitalisation risk was not significantly different between gabapentin and pregabalin for any of the exposure periods.

Male patients demonstrated a slightly lower risk of fracture hospitalisations than female patients for all the exposure periods (Table 9-3), although the difference was only statistically significant for the risk periods for 1-7 days (aIRR in male: 1.01, 95%CI: 0.83, 1.23 vs. aIRR in female: 1.53, 95%CI: 1.37, 1.71) and 29+ days (aIRR in male: 0.71, 95%CI: 0.67, 0.76 vs. aIRR in female: 0.90, 95%CI: 0.87, 0.94).

Table 9-3. SCCS results for subgroup analyses on the risk of fracture hospitalisation for risk periods of gabapentinoid exposure periods

Risk Periods	IRR (95% CI)	aIRR (95% CI)	aIRR (95% CI)
Drug			
Gabapentin			
1-7 days	1.82 (1.60, 2.06)*	1.50 (1.32, 1.70)*	
8-14 days	1.40 (1.21, 1.61)*	1.15 (1.00, 1.33)	
15-28 days	1.18 (1.05, 1.32)*	0.97 (0.86, 1.09)	
29+ days	1.16 (1.11, 1.21)*	0.83 (0.79, 0.87)*	
Pregablin			
1-7 days	1.56 (1.27, 1.90)*	1.28 (1.05, 1.57)*	
8-14 days	1.45 (1.18, 1.79)*	1.20 (0.97, 1.48)	
15-28 days	1.25 (1.06, 1.48)*	1.03 (0.87, 1.22)	
29+ days	1.14 (1.08, 1.22)*	0.82 (0.76, 0.87)*	
Gender			
Female			
1-7 days	1.87 (1.68, 2.09)*	1.53 (1.37, 1.71)*	
8-14 days	1.45 (1.28, 1.64)*	1.18 (1.04, 1.34)*	
15-28 days	1.27 (1.15, 1.40)*	1.03 (0.94, 1.14)	
29+ days	1.29 (1.25, 1.34)*	0.90 (0.87, 0.94)*	
Male			
1-7 days	1.17 (0.96, 1.41)	1.01 (0.83, 1.23)	
8-14 days	1.15 (0.95, 1.41)	1.00 (0.82, 1.22)	
15-28 days	0.95 (0.81, 1.12)	0.83 (0.70, 0.97)*	
29+ days	0.92 (0.87, 0.97)*	0.71 (0.67, 0.76)*	



*Note: (1) * indicates a P-value lower than 0.05; (2) The table presents the association between gabapentinoid exposure risk periods and fracture hospitalisation (reference group: baseline gabapentinoid non-exposure period), after adjusting for age, season, diagnosis of osteoporosis, diagnosis of rheumatoid arthritis and exposures to fracture-related drugs.*

9.4.3. Sensitivity analysis

The sensitivity analyses showed that the results in the primary analysis are robust, especially the higher than baseline fracture hospitalisation risk during the first two weeks of gabapentinoid exposures, because the significantly higher risks of fracture hospitalisation in the 1-7 days and 8-14 days risk periods are consistently observed through all six sensitivity analyses (Table 9-4).

Both sensitivity analyses including a pre-exposure period (sensitivity analysis 1 and 2) identified a very high risk of fracture hospitalisation during the pre-exposure period. The significantly lower than baseline risk of fracture hospitalisation in the 29+ days risk period in the primary analysis was reversed to be significantly higher than baseline in the sensitivity analysis with a 90-day pre-exposure (aIRR: 1.05, 95%CI: 1.01, 1.08).

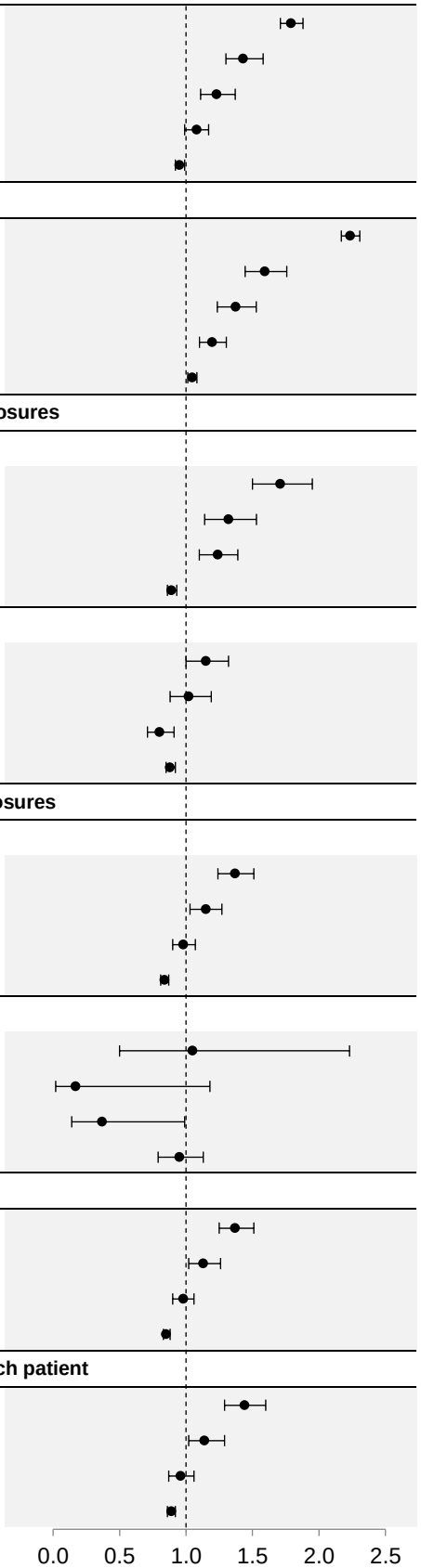
The risk of fracture hospitalisation is higher for the first gabapentinoid exposure than subsequent gabapentinoid exposures for all four risk periods, but the difference is only statistically significant in the 1-7 days risk period (first exposure aIRR: 1.71, 95%CI: 1.50, 1.95 vs. subsequent exposures aIRR: 1.15, 95%CI: 1.00, 1.32) and the 15-28 days risk period (first exposure aIRR: 1.24, 95%CI: 1.10, 1.39 vs. subsequent exposures aIRR: 0.80, 95%CI: 0.71, 0.91).

None of the four risk periods of high-dose gabapentinoid exposure periods was found associated with a higher risk of fracture hospitalisation (Table 9-3), due to the small statistical power limited by the small sample size of high-dose gabapentinoid exposure periods (Appendix 8).

The sensitivity analyses that adjusted for the potential biases of delayed diagnosis of osteoporosis and non-random occurrence of fracture hospitalisations both showed consistent results through all four risk periods with the main analysis (Table 9-4). One noticeable result is that the risk of fracture hospitalisation in periods with osteoporosis (aIRR: 2.86, 95%CI: 2.74, 2.99) becomes higher than the risk for osteoporosis-free periods when the osteoporosis diagnosis date was moved 1 year earlier.

Table 9-4. SCCS results for sensitivity analyses on the risk of fracture hospitalisation for risk periods of gabapentinoid exposure periods

Risk Periods	IRR (95% CI)	aIRR (95% CI)	aIRR (95% CI)
Analysis 1: include a 28-day pre-exposure period			
Pre-exposure period	2.07 (1.97, 2.17)*	1.73 (1.65, 1.82)*	
1-7 days	1.68 (1.52, 1.85)*	1.39 (1.26, 1.53)*	
8-14 days	1.45 (1.30, 1.61)*	1.20 (1.08, 1.33)*	
15-28 days	1.27 (1.16, 1.38)*	1.04 (0.96, 1.14)	
29+ days	1.25 (1.22, 1.29)*	0.90 (0.87, 0.93)*	
Analysis 2: include a 90-day pre-exposure period			
Pre-exposure period	2.61 (2.53, 2.69)*	2.24 (2.17, 2.31)*	
1-7 days	1.92 (1.74, 2.11)*	1.59 (1.44, 1.76)*	
8-14 days	1.65 (1.49, 1.84)*	1.37 (1.24, 1.53)*	
15-28 days	1.44 (1.33, 1.57)*	1.20 (1.10, 1.30)*	
29+ days	1.44 (1.39, 1.48)*	1.05 (1.01, 1.08)*	
Analysis 3: separate the first exposures from subsequent exposures			
First exposure			
1-7 days	1.85 (1.63, 2.11)*	1.70 (1.49, 1.93)*	
8-14 days	1.43 (1.23, 1.65)*	1.31 (1.13, 1.52)*	
15-28 days	1.34 (1.20, 1.50)*	1.23 (1.09, 1.37)*	
29+ days	1.07 (1.03, 1.11)*	0.86 (0.83, 0.90)*	
Subsequent exposures			
1-7 days	1.46 (1.27, 1.68)*	1.10 (0.96, 1.26)	
8-14 days	1.30 (1.12, 1.51)*	0.98 (0.84, 1.14)	
15-28 days	1.02 (0.90, 1.15)	0.77 (0.68, 0.87)*	
29+ days	1.27 (1.22, 1.32)*	0.82 (0.79, 0.85)*	
Analysis 4: separate high-dose exposures from low-dose exposures			
Non-high-dose			
1-7 days	1.64 (1.49, 1.81)	1.37 (1.24, 1.51)*	
8-14 days	1.36 (1.22, 1.51)	1.15 (1.03, 1.27)*	
15-28 days	1.17 (1.08, 1.27)	0.98 (0.90, 1.07)	
29+ days	1.17 (1.13, 1.21)	0.84 (0.81, 0.87)*	
High-dose			
1-7 days	-	1.05 (0.50, 2.23)	
8-14 days	-	0.17 (0.02, 1.18)	
15-28 days	-	0.37 (0.14, 0.99)	
29+ days	1.81 (1.43, 2.28)	0.95 (0.79, 1.13)	
Analysis 5: move the osteoporosis diagnosis 1 year earlier			
1-7 days	1.64 (1.49, 1.80)*	1.35 (1.23, 1.49)*	
8-14 days	1.35 (1.22, 1.50)*	1.12 (1.00, 1.24)*	
15-28 days	1.17 (1.07, 1.27)*	0.96 (0.88, 1.04)	
29+ days	1.17 (1.14, 1.21)*	0.82 (0.80, 0.85)*	
Analysis 6: include only the first fracture hospitalisation of each patient			
1-7 days	1.63 (1.47, 1.81)*	1.41 (1.27, 1.56)*	
8-14 days	1.30 (1.15, 1.46)*	1.12 (1.00, 1.26)*	
15-28 days	1.09 (0.99, 1.20)	0.94 (0.86, 1.04)	
29+ days	1.09 (1.05, 1.13)*	0.85 (0.82, 0.88)*	



*Note: (1) * indicates a P-value lower than 0.05; (2) The table presents the association between gabapentinoid exposure risk periods and fracture hospitalisation (reference group: baseline gabapentinoid non-exposure period), after adjusting for age, season, diagnosis of osteoporosis, diagnosis of rheumatoid arthritis, exposure to fracture-related drugs.*

9.5. Discussion

The study results suggest that 1-7 days and 8-14 days of a gabapentinoid exposure have significantly higher risks of fracture hospitalisation, while the risk of fracture hospitalisation in the 29+ days risk period of the exposure is significantly lower than non-exposure baseline periods. The results also suggest that the fracture hospitalisation risk in the first-ever gabapentinoid exposure period for each patient is higher than any subsequent exposure periods. No dose-dependent association was observed between gabapentinoid exposure and fracture hospitalisation, due to the small sample size of high-dose gabapentinoid users.

The sensitivity analyses showed a significantly high risk of fracture hospitalisation in both the 14-day and the 90-day pre-exposure periods, strongly indicating the existence of event-dependent gabapentinoid exposure. The fracture hospitalisation risk in the 29+ days risk period was lower than baseline in the primary analysis, but this reversed into a significantly higher risk in the sensitivity analysis with a 90-day pre-exposure period. Therefore, it is likely that the lower than baseline risk for the 29+ days risk period in the primary analysis is due to bias from event-dependent gabapentinoid exposures. However, since the mechanism of fracture-dependent gabapentinoid exposures has not been investigated, the primary analysis result of a lowered risk of fracture hospitalisation in the 29+ days risk period cannot be fully dismissed.

The sensitivity analysis also suggested a potential underdiagnosis of osteoporosis in the study cohort because the negative association between osteoporosis and risk

of fracture identified in the primary analysis became positive when the diagnosis date was moved 1 year earlier than the recorded date. This suggests that it may be beneficial for clinicians to be mindful of patients' osteoporosis risk or bone mass index before prescribing gabapentinoids.

This is the first study to evaluate the risk of fracture hospitalisation during gabapentinoid exposures in patients with CNCP. One available study evaluated the risk of fracture-relevant outcomes in pregabalin users but not gabapentin users. Miyamoto *et al.* (2020) conducted a case-control study on 89,899 patients over 20 years old from January 2014 to December 2016 using the Japan Medical Data Centre claims database [296]. The study identified a significant association between being prescribed pregabalin in the 180 days prior and injury including fractures (aOR: 1.22, 95%CI: 1.06, 1.40) [296]. Since the injury outcome in *Miyamoto*'s analysis included hip fractures, wrist fractures, lower leg fractures, humeral fractures, and head injuries, the results suggest a link between fracture and preceding pregabalin exposures, which is in line with the findings of this study.

In addition to the case-control study, Miyamoto *et al.* (2020) also conducted a case cross-over study using the same study cohort and found pregabalin use in the 30-days before (aOR, 1.48; 95% CI, 1.10, 2.00) and in the 15-days before (aOR: 1.92, 95%CI: 1.43, 2.59) the injury were both significantly associated with an increased risk of injury. This result indicates a high risk of injury a short time after pregabalin initiation. Although *Miyamoto's* study was for injury and only studied the effect of pregabalin exposure, the results were consistent with the findings of this study.

No association was observed between fracture hospitalisation and high-dose gabapentinoid exposure, due to a limited sample size, but high-dose gabapentinoid exposure is not free from risk, as demonstrated in Chapter 8. Previous studies have

identified a dose-dependent risk of hospital visits caused by falls and fractures in gabapentinoids. Muanda *et al.* (2022) conducted a cohort study of 74,084 adults aged over 66 years who had chronic kidney disease (CKD) and were not receiving dialysis. This study compared the risk of hospital visits caused by multiple outcomes in the 30 days after a new gabapentinoid prescription between high-dose (gabapentin >300 mg/d or pregabalin >75 mg/d) and low-dose gabapentinoid exposures [267]. The results showed no significant difference in the 30-day risk of hospital visits due to fracture between high-dose and low-dose gabapentinoid exposure (aRR: 1.14, 95%CI: 0.91, 1.43), probably due to a similarly small sample size of fracture (n=143, 0.47%), as in this study. However, the 30-day risk of hospital visits due to falls was higher in patients exposed to high-dose gabapentinoids than low-dose gabapentinoids (aRR: 1.19, 95%CI: 1.04, 1.37) [267].

Since gabapentinoid-related fractures are assumed to be caused by falls as a result of the dizziness side effect, it is reasonable to extrapolate from Muanda's result and hypothesise that high-dose gabapentinoid exposure could be associated with a higher fracture hospitalisation risk. This could be investigated if a sufficient sample size for fracture hospitalisation in high-dose gabapentinoid users with CNCP becomes available.

Although gabapentinoids are not recommended for fractures in the National Institute for Health and Care Excellence (NICE) clinical guidelines [297, 298], it was found to be frequently used after fractures in this study, potentially to relieve acute pain. Since the NICE guidelines for fracture were last updated in 2016, the concept of using gabapentinoids for acute pain after fracture may have been widely accepted in recent years, before being adopted by guidelines. However, whether gabapentinoids are effective for acute pain after fracture is not clear [299]. A US randomised controlled trial comparing gabapentin versus placebo on acute pain for

critically ill patients with rib fractures (n=40) suggested that gabapentin treatment for up to one month did not improve acute outcomes such as daily numeric pain scores and opioid consumption [300]. Further studies are needed to evaluate the effect of gabapentinoids on acute fracture pain.

This study conducted a comprehensive confounding adjustment to ensure the results are not biased by unmeasured confounders. The SCCS study design naturally adjusts for time-invariant variables by using patients as their own control, while other influential time-varying factors were adjusted manually in the analysis. This study enables the comparison of fracture hospitalisation risk for different time periods of a gabapentinoid exposure, which is not easily achievable using other study designs. This study included six sensitivity analyses to consider possible violations of the model assumptions, especially the assumption of no event-dependent occurrences, and thus improve the robustness of the primary analysis. A data imputation algorithm (Section 8.3.3) was used to measure the gabapentinoid exposure episodes and therefore ensure the exposure periods were defined accurately.

There are some limitations in this study. Firstly, only fracture hospitalisations recorded in secondary care databases were included in this study. It is likely that many gabapentinoid-related fractures are managed in primary care, outpatient services, and A&E and were thus not included in this study. Therefore, the risk of all fractures in the 1-7 days of gabapentinoid exposures could be much higher than the 1.4 times observed in this study. Secondly, although time-varying factors associated with fractures such as age, season, osteoporosis, rheumatoid arthritis, and fracture-related drugs had been adjusted for in the SCCS analysis, there could still be influential unmeasurable time-varying factors not included, as this study has a long follow-up time. For example, changes in patients' lifestyles such as smoking,

drinking, and physical activity, and some rare diseases that can cause fractures such as Parkinson's disease [301]. Thirdly, there is evidence that the no event-dependent exposure assumption of SCCS is violated in this study [302]. Although a pre-exposure period was applied in the sensitivity analyses to mitigate this violation, it is still worth acknowledging that the assumption may be violated, and the mechanisms for fracture-dependent gabapentinoid exposures should be investigated in future studies. Fourthly, there may be misclassification in the gabapentinoid exposure periods because drug utilisation patterns derived in an epidemiological study have many assumptions, such as patients dispensing the prescriptions, taking the prescribed medicines from the date of prescription, taking all prescribed medicines, and exposure continuing during the gaps between prescriptions within a single episode.

In summary, exposure to gabapentinoids in patients with CNCP is associated with a 1.4 times higher risk of fracture hospitalisation in the first week of exposure and a 1.1 times higher risk in the second week, compared to non-exposure baseline periods. The risk of fracture hospitalisation decreases at later times in an exposure. Restarting gabapentinoid treatment is less likely to result in fracture hospitalisations than the first treatment. The findings suggest that initiation of gabapentinoids for patients with CNCP who have not previously been prescribed gabapentinoids should be done only after a careful evaluation of patients' fracture risk, and should follow a carefully monitored titrating process to build up tolerance to side effects.

Chapter 10. Discussion and implications

10.1. Introduction

This PhD project aims to evaluate drug safety issues in gabapentinoid users with CNCP and support interventions on gabapentinoid utilisation in English primary care. This chapter includes a summary of the key findings from the six study chapters and a discussion about the interpretation and implication of the study results at a broader level.

10.2. Summary of main findings

This PhD project adopted an epidemiological approach to test the hypotheses about the safety of gabapentinoid use in patients with CNCP in English primary care. The results showed that: (1) general practices in the North of England, where people are more likely to have a deprived socioeconomic status, had a higher prescribing rate of gabapentinoids in the past decade; the 2019 national policy of gabapentinoid classification affected these practices the most; (2) gabapentinoid users in the CNCP population have a higher risk of the serious adverse events of drug-related deaths, suicides, and fracture hospitalisations after gabapentinoid initiation; (3) a further increased risk of the serious adverse events in gabapentinoid users with CNCP is attributable to high-dose exposures to gabapentinoids; (4) the first two weeks of gabapentinoid exposures have a much higher risk of fracture hospitalisation than time periods with no gabapentinoid exposure. The findings of the studies identify the gabapentinoid users at higher risk and provide information for future interventions to reduce the harms of gabapentinoids.

10.2.1. The impact of the gabapentinoid classification policy

The gabapentinoid classification policy was implemented in the UK in April 2019 to reduce the misuse and abuse of gabapentinoids [303]. However, the effect of the policy on gabapentinoid prescribing, misuse, and abuse has not been investigated before. This project addressed this evidence gap, and found the gabapentinoid classification policy was effective at reducing gabapentinoid prescribing in English general practices.

Before the gabapentinoid classification policy, gabapentinoid prescribing in English general practice increased from 2800 to 4773 DDDs/1000 people between 2013 and 2019 (Chapter 3). The classification of gabapentinoids in April 2019 significantly slowed down the previously increasing trend of gabapentinoid prescribing at both levels (β_2: -25.23; 95%CI: -38.78, -11.69) and trend (β_3: -1.89; 95%CI: -2.67, -1.12; P<0.001) (Chapter 4). The reduction in gabapentinoid prescribing after the classification indicates that the gabapentinoid classification policy may have discontinued some unnecessary gabapentinoid prescriptions, and guided clinicians to be more cautious in gabapentinoid initiation.

In addition, the general practices with the highest levels and the greatest increases in gabapentinoid prescribing after 2013 are mainly located in the north of England and along the east and south coastline (Chapter 3). These practices experienced the largest drop in prescribing after the gabapentinoid classification policy (Chapter 4), indicating that future regional interventions can be implemented to prevent gabapentinoid-related harm (Section 10.4.2).

Although the motivation of the classification policy was to reduce gabapentinoid misuse and abuse, the increasing prescribing trend after the policy indicates that the

risk of gabapentinoid misuse and abuse has not been completely removed. Therefore, further study was conducted to investigate the potential harms relevant to gabapentinoids, as well as the risk factors of gabapentinoid-related safety issues to help reduce harm.

10.2.2. Gabapentinoid's association with serious adverse events

Although previous studies assessed the risk of serious adverse events relevant to gabapentinoids [20, 22, 23], the incidence rate of serious adverse events had not been investigated for gabapentinoid users, and the association between gabapentinoids and serious adverse events had not been evaluated in the CNCP population. This project addressed the evidence gap by identifying the incidence rates of drug-related death, suicide death, suicide hospitalisation, and fracture hospitalisation for gabapentinoid users, and found they were higher than for gabapentinoid non-users in the CNCP population. The association between gabapentinoid exposure and these serious adverse events was also evaluated.

This project started the investigation of gabapentinoid safety by understanding how gabapentinoids are initiated in patients with CNCP, because the patients' characteristics can be informative for the adverse events that need more attention. In Chapter 6, gabapentinoid users with CNCP were found to have a mean age of 55.91 years, are more likely to be female (62.7%), and tend to have a poorer socioeconomic status than the UK average. A significantly higher percentage of gabapentinoid users than non-users had baseline comorbidities and pain medication use. Previous opioid or antidepressant uses are both influential factors associated with gabapentinoid initiation, which possibly indicates unsatisfied pain management before gabapentinoid initiation. The baseline demographics of gabapentinoid users and the influential factors associated with gabapentinoid

initiation are risk factors for some of the serious adverse events identified in previous literature. Therefore, further studies investigated the risk of serious adverse events relevant to gabapentinoids.

In the following matched cohort study (Chapter 7), the IRRs and the log-rank tests suggested that the risk of drug-related death, suicide death, suicide hospitalisation, and fracture hospitalisation are significantly higher for gabapentinoid users with CNCP compared to non-users. After adjusting for baseline demographics and pain medication use, exposure to gabapentinoids is still associated with increased risks of the serious adverse events. However, the exposure to gabapentinoids could vary between patients because the recommended daily doses for gabapentinoids have a broad range. Patients can utilise gabapentinoids in many different patterns, such as taking them for a long time or with other pain relief medicines. Therefore, it was hypothesised that different utilisation patterns of gabapentinoids could contribute differently to the increased risk of drug-related death, suicide death, suicide hospitalisation, and fracture hospitalisation.

10.2.3. The risk profile of gabapentinoid use

Previous studies identified a dose-dependent risk of fracture with gabapentinoids [101], but the effect of different gabapentinoid uses (i.e. different utilisation patterns) on the risk of the serious adverse events had not been investigated in the CNCP population. This project addressed this evidence gap by identifying a higher risk of the serious adverse events for high-dose gabapentinoid users compared to non-high-dose users, and also identified the risk periods in gabapentinoid exposures that have a higher risk of fracture hospitalisation.

To investigate the association between different gabapentinoid use and the serious adverse events, gabapentinoid utilisation patterns were assessed in Chapter 8. The study found that persistent gabapentinoid exposures are common in gabapentinoid users with CNCP (26.3% of all gabapentinoid exposure episodes), while high-dose gabapentinoid exposures are rare (1.6% of all gabapentinoid exposure episodes). Concurrent exposures with opioids (56.5%) and concurrent exposures with antidepressants (49.1%) are common in gabapentinoid users with CNCP. Half of the high-dose gabapentinoid users were found to continue their first gabapentinoid exposure for over 360 days. In contrast, half of the non-high-dose users discontinued their first gabapentinoid exposure by day 58. This finding indicates that persistent gabapentinoid use could build up to high-dose use, which is a risk factor for the serious adverse events. Therefore, it was hypothesised that high-dose gabapentinoid exposure is associated with a higher risk of the serious adverse events.

After considering the baseline characteristics and the effect of persistent gabapentinoid exposure, high-dose gabapentinoid exposure was found to be associated with drug-related death (aHR: 1.40, 95%CI: 1.20, 1.63), suicide death (aHR: 1.29, 95%CI: 1.12, 1.49), suicide hospitalisation (aHR: 1.07, 95%CI: 1.00, 1.15), and fracture hospitalisation (aHR: 1.11, 95%CI: 1.05, 1.17) (Chapter 8). This finding could inform clinicians about the risk of high-dose gabapentinoid exposure (Section 10.4.1).

Since there is evidence of a quick onset of fracture following gabapentinoid exposure as a result of the dizziness side effect, a further study was conducted to investigate the risk of fracture hospitalisation in different time periods of gabapentinoid exposures. It was found that the risk of fracture hospitalisation is the highest in the first week of gabapentinoid exposures (aIRR: 1.36, 95%CI: 1.24,

1.50), followed by the second week (aIRR: 1.13, 95%CI: 1.01, 1.25), when compared to the baseline period after adjusting for time-varying confounding factors. This finding provides evidence for clinicians to potentially reduce fracture hospitalisation following gabapentinoid prescription (Section 10.4.1).

10.3. Strengths and limitations

10.3.1. Using pharmacoepidemiological approaches

Strengths

The pharmacoepidemiological study approach adopted in this project enables the study of real-world prescribing trends of gabapentinoids and the high-risk utilisation patterns of gabapentinoids at a population level. The results of this epidemiological project addressed the evidence gap by providing population-level evidence about the misuse and abuse potential of gabapentinoids, which serves as a bridge between pharmacological evidence [14, 304] and post-mortem or clinical case evidence [104, 108, 305, 306]. It estimates the incidence rates of serious adverse events in gabapentinoid users that are not observable in clinical trials due to their low incidence rates and the long period needed for observation [307].

The strength of pharmacoepidemiological studies is that they use real-world data, which is normally large in size and has long follow-up times, to support clinical findings on the usage, benefits and risks of medication [308]. The use of real-world data provides evidence at a broader population level compared to other approaches such as randomised controlled trials. As a result, they can identify rare adverse events and associate them with medication use that could not normally be accomplished by other study approaches as demonstrated in this project. The real-world evidence generated by pharmacoepidemiological studies had been adapted for regulatory decision-making on drug safety in Europe, the US and Canada [309-

311]. There has also been a growing interest in applying the real-world evidence generated in pharmacoepidemiological studies to evaluate the efficacy and safety of medications to support new approvals or additional indications by regulatory agencies [312].

Limitations

Although the use of pharmacoepidemiology in drug safety research and postapproval surveillance had been widely acknowledged [309-311], it does have limitations. Firstly, randomisation in randomised clinical trials that aim to achieve an even distribution of confounding factors between cohorts is not feasible in pharmacoepidemiological studies. Instead, cohort matching and confounding adjustment are commonly used to mitigate the unbalanced patient allocation problem. However, the confounders of interest in pharmacoepidemiological studies are not always recorded in secondary databases because these databases are not designed for research purposes. Similarly, the study outcomes, especially mild adverse events, may not be closely monitored and recorded by clinicians during routine clinical practice. Therefore, unobserved confounders and outcomes are known limitations of pharmacoepidemiological studies which will also have influenced the results of this project.

Secondly, pharmacoepidemiological studies highly rely on statistical analyses and models that each have different theories and assumptions, so the results can be highly dependent on statistical model selection. There could be many reasonable statistical approaches for a single study question, but the results from different approaches sometimes conflict [312]. To illustrate this issue, Silberzahn *et al.* (2018) sent the same dataset to 29 research teams involving 61 analysts to address the same study question “whether soccer referees are more likely to give red cards

to dark-skin-toned players than to light-skin-toned players" [313]. Twenty teams (69%) found a statistically significant positive effect and nine teams (31%) did not observe a significant relationship, with the estimated effect sizes ranging from 0.89 to 2.93 (median = 1.31) in odds-ratio units [313]. A good way to improve the reliability of results generated in epidemiological studies is to integrate different study designs to triangulate the effect estimations [312]. In this project, the risk of fracture hospitalisations had been tested in cohort studies and a self-controlled case-series study. Both study designs resulted in positive association results, so the association between gabapentinoids and fracture hospitalisations is comparatively robust. Further studies that use different databases and apply different analytical methods are expected to build on and address limitations of this project.

10.3.2. Using secondary healthcare databases

Strengths

Secondary databases contain patient care data routinely gathered for administrative purposes, not for answering specific study questions in the manner of primary data collection does [284]. The use of secondary databases in this project enabled the study of utilisation patterns and the incidence of rare adverse events in gabapentinoid users, which could not be achieved using other data sources due to their small sample size and limited patient information. This project used Electronic Health Records (EHRs), patient registries and pharmacy dispensing data as the secondary data sources. The English national prescribing database, a pharmacy dispensing database released monthly by the NHS, was used to study the national prescribing trend of gabapentinoids, potential practice-level harms of gabapentinoids and the impact of gabapentinoid classification at the general practice level. The CPRD patient-level EHR database was used to study the user characteristics of gabapentinoids in English primary care. External databases

including the HES APC, the ONS Death Registration and the ONS 2015 IMD were linked to the CPRD to study serious adverse events associated with gabapentinoids.

A major strength of applying secondary databases for pharmacoepidemiological studies is that they provide rich data covering many aspects of patients' information for a large population [314]. When the secondary databases used in a study project are complementary in their patient coverage or are linkable to achieve more complete health information per patient, the benefits of large databases are even stronger.

Good drug utilisation pattern research usually relies on detailed prescription information in a large population, which can only be supplied by secondary databases because primary data collection normally cannot collect such a large amount of detailed prescription data within a limited time and budget [284]. The prescribing data in CPRD provides detailed information about each prescription, including product information such as the formulation and strength, the date of the prescription, the quantity prescribed, the daily dose suggested by the GP and the duration covered by the prescription. This detailed information makes observing the gabapentinoid utilisation patterns and associating them with adverse events possible. Similarly, the English national prescribing data and the number of patients registered with GP practice data from the NHS provide the monthly practice-level prescribing quantity of individual products with product information and the monthly number of patients registered with a GP practice. Thus, the monthly practice prescribing rate of gabapentinoids can be calculated and mapped for England. In addition to prescribing data, the clinical data in CPRD provides a variety of patient information that forms the baseline characteristics and confounding factors in the analysis of serious adverse events of gabapentinoids.

Secondary databases with different patient coverage combined together could provide more powerful study results than either alone. In this project, the NHS national prescribing data is complementary to CPRD primary care data in patient coverage, so the results of the studies using both data sources are more solid. CPRD is an individual-level EHR database that covers around 18 million currently registered patients in the UK. Although it has a large sample of patients that are representative of the UK population in terms of age and sex [182], it is not guaranteed that the results generated from the CPRD are free from sampling bias. However, when the studies using CPRD data are supported by consistent results generated from NHS England national prescribing data, the results are more robust than those using individual databases. For example, socioeconomic status and comorbidities were found to be associated with the prescribing of gabapentinoids at both individual-level sampled data and aggregated-level national data, so the association was more robust.

Secondary databases linked through anonymised patient identifiers can provide a more comprehensive patient profile and facilitate more complex studies. CPRD is a primary care database that collects patient electronic health records in general practices, so information regarding secondary care, death registry and socioeconomic status which are not relevant to primary care service is not routinely recorded in CPRD [188]. However, the linking of CPRD data to external databases such as HES-APC, ONS Death Registrations and the ONS 2015 IMD provides a more complete patient profile and therefore facilitates observational studies that require study outcomes outside of primary care and influential factors (e.g. socioeconomic status) that are not recorded in primary care databases.

Another strength of secondary databases is that they provide a long follow-up time for observational studies. The observation of drug utilisation patterns and some rare adverse events sometimes needs a longer follow-up time than that of the majority of randomised controlled trials and primary data collection. Secondary databases can usually provide a long follow-up period to enable the observation of these study outcomes. Patients in CPRD GOLD had a median follow-up time of 9.4 years (IQR: 3.4-13.9) for active patients in 2015 [182]. Around 20% of the active patients in CPRD had over 20 years of follow-up as measured in October 2022 [188]. The identification of persistent gabapentinoid users and the serious adverse events after exposure to gabapentinoids need long follow-up times, starting from the diagnosis of CNCP in this study, which can only be supported by secondary databases that provide such long follow-up times for patients.

Limitations

Although secondary databases have many strengths, the data in them are not collected for research purpose and therefore has limitations when used for research. The limitations of secondary databases detailed below mainly apply to the CPRD individual-level database because the NHS national prescribing aggregated-level database provided only practice-level monthly prescribing data, which was inspected and cleaned by NHS before being published.

Firstly, the estimation of drug utilisation patterns using secondary databases assumes patients dispensed and took the drugs at the prescription date, but secondary databases can only capture the behaviour of prescribers, not of patients. The assumption is an exaggeration of good patients' adherence, as non-adherence to pain medication is known to be common in the chronic pain population [315]. This common assumption of patient drug use in pharmacoepidemiology introduces bias

into study results and therefore the study results regarding the utilisation of gabapentinoids using CPRD databases (i.e. Chapters 6-9) should be presented well informed with this bias.

Secondly, the completeness of data in secondary databases could be low. The risk factors that were considered important in pharmacoepidemiological research such as body mass index, smoking status, alcohol consumption and some mild symptoms and diseases were not necessarily recorded in routinely collected administrative databases (i.e. CPRD in this project) and were highly influenced by local health care policies [284]. Meanwhile, some coded information in secondary databases was processed from free text using techniques such as the natural language process, which is highly dependent on the special techniques adapted by the database processor and could unavoidably miss some information from the free texts [284]. For example, the daily dose information in the prescription data of CPRD was processed from free text typed in during GP consultations, and the missing rate of the prescription daily dose was comparatively high. Although a data imputation algorithm was applied to solve the missing daily dose issue, the imputed data was an estimation rather than the actual data and could potentially bias the study results.

Thirdly, the quality of secondary data is not guaranteed because the databases are not intended for specific research purposes [316]. It is common to have typos or misreported information in administrative databases because no validation process was required for these databases, while in comparison randomised controlled trials monitored data quality much more rigorously. The data quality issue in secondary data occurs less when data are presented in codes (e.g. disease code and product codes), but was more likely to exist in numeric format data. For example, the quantity of prescription could be mistyped by the GP as “1220” by accidentally

adding an extra 2 instead of the intended “120” tablets. A data cleaning process that removes outliers in numeric format data was applied in this project to maximally solve the data quality issue, but data cleaning could not guarantee all low-quality data were spotted.

10.3.3. Selection of the study population

The selection of the study populations in this project was based on the coverage of the databases and the aim of the project. The study population in Chapters 3 and 4 was patients registered with a GP practice in England between April 2013 and May 2020. The study cohorts in Chapters 6-9 all embedded in the CNCP population in English primary care identified in Chapter 5, which was defined as adult patients who had a new occurrence of CNCP between 1 January 2005 and 31 December 2019, had no history of cancer and were eligible for the CPRD external link eligible dataset.

Strength

The strength of studying all patients registered with GP practices in England in Chapters 3 and 4 is that it included all people of interest rather than sampling from the target population, so the prescribing results would not have sampling bias. The strength of selecting the CNCP population in chapters 6-9 using individual-level data was that it focused on a specific patient group and reduced the sample size of the main study cohorts from all gabapentinoid users to gabapentinoid users with CNCP to avoid occupying excessive calculation power.

Limitations

However, there are limitations about selecting the above study populations. Firstly, the study population in this study were within primary care settings, assuming primary care is the main source of gabapentinoid prescriptions. This assumption was made because long-term management of chronic pain was mostly conducted in primary care in the UK [5]. The gabapentinoids accessed from other sources such as secondary care, patient diversion and the black market were not accounted for in this project. The gabapentinoid prescriptions from secondary care services are likely to be short-term, so the study results might not be largely influenced without including the prescriptions from secondary care. However, large quantities of gabapentinoids could have been sourced elsewhere, and gabapentinoids from these sources could be more associated with drug abuse and drug harm [119]. Kalk *et al.* (2022) conducted a post-mortem study using coroner-reported information from the National Programme on substance abuse deaths in England up till November 2021. The study found that among the 2,808 cases that had opioids and gabapentinoids co-detected, a total of 772 decedents (25.3%) were co-prescribed a gabapentinoid and an opioid according to their GP records [108], indicating most of the cases were not actually prescribed the detected drugs in primary care. Vikas *et al.* (2014) conducted an online questionnaire survey about gabapentinoids misuse including 1,500 people between 16 and 59 years in 2013 in the UK [317]. Among the responders that self-reported misusing gabapentinoids, 63.1% reported receiving gabapentinoids from health services, 57.8% from family or acquaintances, 47.3% from the Internet and 7.8% from abroad, while 36.8% obtained their supply from multiple sources [317]. The gabapentinoids accessed outside the health service system would probably cause more harms than those prescribed in primary care but were not studied in this study. In addition, the misuse of gabapentinoids in UK prison settings had also been a concern [318]. Therefore, the actual risk

attributable to gabapentinoids may be higher than the results in this project due to this limitation of the study cohort.

Secondly, the CNCP study population in the Chapters 6-9 were limited to the patients who were diagnosed with CNCP and therefore were limited in extrapolation. Although CNCP was the target population that was most concerned with the safety issue of gabapentinoids, the results in this study were not applicable to patients with anxiety, focal seizures, and other indications of gabapentinoids Therefore, the results should be interpreted and applied to clinical practice with caution of the target population.

10.3.4. Developing code lists for health conditions

Code lists are important tools to extract data from secondary databases. The code lists for drugs are easy to define by chemical substances and identify directly from the code browser of CPRD databases. In contrast, code lists for comorbidities and adverse events are complicated because the definition of a disease could vary between research groups and between different study questions. The read code lists for comorbidities in CPRD GOLD used in this project were mostly referenced from publicly available code lists developed by other researchers. The comorbidity code lists for Aurum were matched using an algorithm generated for this project. Only the code lists for chronic pain were generated from scratch specifically for this project following a code generating algorithm. The ICD-10 codes for the serious adverse events were referenced from published studies.

Strengths

The strength of generating chronic pain code lists from scratch rather than adapting published code lists is that they fit better with the study questions and the definition of chronic pain in this project. The strength of referencing code lists for comorbidities and adverse events from published studies is that the code list was peer-reviewed and has higher reliability and also it saved much time in the data processing procedure of this project. The strength of using the NHS data immigration tool to match GOLD read code lists to Aurum SNOMED CT code lists is the definition of the comorbidities was consistent between the two databases.

Limitations

A general limitation of the code lists for comorbidities is that the coverage is hard to be inclusive of all the disease diagnoses using a keyword searching strategy and while the disease code library grows over time as new codes were added. The limitation of generating chronic code lists from scratch is that it was not thoroughly validated by cross-validation across different databases. The limitation of referencing code lists from published studies may sometimes not fit well with the specific study questions. The limitation of bridging the GOLD comorbidity code lists to Aurum is that the matching procedure was newly generated and had not been validated.

10.3.5. Matching technique for cohort identification

Strength

A simple matching by age, gender and practice was conducted at the cohort selection in Chapter 6 to identify the gabapentinoid non-user cohort. One strength of matching is that it reduced the sample size of gabapentinoid non-users to save

computational power and increase the efficiency of the analysis [319]. Another strength of matching is that it made the two cohorts have a balanced distribution of age, gender and geographical location (i.e. practice), resulting in the matched factors independent of gabapentinoid exposure [320]. The strength of simply matching on age, gender and practice is that it allowed the exploration of influential factors that could associate with the prescribing of gabapentinoids [320]. Since the confounding factors of prescribing gabapentinoids had not been fully studied before, simply matching on age, gender and practice which are reportedly associated with prescribing gabapentinoids in other studies [129] would leave more space for confounder exploration.

Limitations

The matching process facilitating a matched cohort study rather than a case-control study does not normally introduce bias and therefore had few limitations [222]. The matching of age, gender and practice cancelled out the chance to identify the actual relationship between these factors and prescribing gabapentinoids as well as the serious adverse events.

10.4. Implications

10.4.1. Implications for clinical practice

Risk factors for gabapentinoid safety issues

This project indicated a higher risk of serious adverse events in gabapentinoid users with CNCP than non-users and identified several risk factors that were associated with higher risk. It found that high-dose gabapentinoid users were at particularly high risk compared to patients who did not take gabapentinoids over the maximum

recommended daily dose. The persistent use of gabapentinoids was found to be a potential reason for building up to high-dose use. It also suggested that the first two weeks of gabapentinoid exposure increase the risk of falls and fracture hospitalisations. These findings suggest there should be a cautious assessment of patients' needs before initiating gabapentinoids for chronic pain, with particular consideration given to long-term and high-dose gabapentinoid use and high-risk time periods during gabapentinoid exposures.

The gabapentinoid utilisation patterns identified in this project suggested a high concurrent use rate of other pain relief medicines with gabapentinoids, especially opioids and antidepressants. The concurrent use of pain relief medicines to relieve chronic pain could easily lead to polypharmacy in old people who have other chronic diseases. Although the risk of concurrent use of gabapentinoids and opioids was not a focus in this project, published studies suggested a high risk of opioid-related deaths when gabapentinoids were concomitantly prescribed in the 120 days preceding the opioid death [22, 23]. Therefore, the concurrent use of gabapentinoids and opioids needs more careful assessment.

Careful prescribing of gabapentinoids

Gabapentinoids are recommended as first-line therapy for neuropathic pain by NICE guidelines [44], but they are not recommended as the first-line therapy for primacy chronic pain (i.e. chronic pain has no clear underlying condition, or where the pain or its impact is out of proportion to any observable injury or disease) [5]. However, the current use of gabapentinoids in managing chronic pain is often off-label and is not always following the guideline recommendations [321]. According to a qualitative descriptive study of 43 US prescribers, pharmacists, or drug policy experts in 2021, gabapentinoids are often prescribed as an alternative to opioids

due to regulatory pressure or in fear of opioid-related harms (e.g. overdose fatalities) [322]. The interviewees in this study express lower concern about gabapentinoid safety [322].

The belief that gabapentinoids have negligible risk is a myth: this project identified a high rate of serious adverse events in gabapentinoid users with CNCP, especially in those with a history of psychoactive substance misuse or alcohol use problems. Therefore, it is recommended that clinicians carefully evaluate both the benefits and risks before initiating gabapentinoids, and proactively consider non-pharmacological approaches for chronic pain such as physical activity and psychological therapy [5]. If the use of gabapentinoids is considered appropriate after a comprehensive evaluation, close follow-up of gabapentinoid and concurrent pain-related medicine use should be put in place to prevent misuse and harm. Some patients were found to therapeutically self-mediate gabapentinoids to treat pain, anxiety, or withdrawal from other drugs or non-therapeutically misuse gabapentinoids for recreational effects [322]. Clinicians should thus be alert to the potential of gabapentinoid misuse by methods such as “doctor shopping”.

Fracture prevention in gabapentinoid users

The high fracture hospitalisation risk at the initiation of gabapentinoids suggests clinicians and pharmacists should pay extra attention to patients with high fracture risks such as the elderly and those with osteoporosis. Gabapentinoid titration and fracture risk evaluation at gabapentinoid prescription could be implemented to help prevent fractures.

A titration process at the drug initiation is recommended for both gabapentin and pregabalin to mitigate the common side effects [8]. For example, the recommended

gabapentin titration schedule is to start with 300 mg on day one, then increase by 300 mg/day until day three (900 mg/day), then further increase in steps of 300 mg every 2-3 days divided into 3 doses per day to maximise efficacy [8]. This titration process should be clearly explained to patients at the prescription by the GP and at dispensing by the pharmacist so that the titration is done properly to minimise the dizziness, drowsiness, and decreased concentration side effects of gabapentinoids. Handouts about the titration process could help with patients' understanding. Individualised titration processes such as taking gabapentinoids four times a day instead of the recommended three times a day could also be applied to achieve better tolerance to the dizziness side effect [323].

Patients' fracture risk should be evaluated before prescribing gabapentinoids and extra advice should be given to those with high risk to reduce falls and fractures. There had been many fracture risk evaluation tools such as FRAX® developed by Kanis *et al.* (2020) to estimate the 10-year probability of hip and major osteoporotic fracture [324] and the Fracture Risk Evaluation Model developed by Rubin *et al.* (2018) to identify patients with imminent risk of fractures using EHRs [325, 326]. Osteoporosis is one of the dominating risk factors in these fracture risk evaluation tools and was found to be highly relevant to fracture hospitalisation in gabapentinoids users but was underdiagnosed. Therefore, a bone density test could be considered at the gabapentinoid initiation if the patient is at high risk of osteoporosis. Fracture-prevention interventions such as physical exercise, environmental assessment and modifications (e.g. home flooring, home check, and home safety devices) and assistive technology (e.g. hip protectors, walking aids) could be recommended to patients at higher fracture risk [327].

Use of the clinical decision support system

The clinical decision support system (CDSS) had been widely used to decrease medication errors by integrating reminder and alerting systems to EHRs or community pharmacy electronic dispensing systems [328]. It has proved effective in many medical procedures such as increasing the prescription rate of statin to patients with atherosclerotic cardiovascular disease [329], reducing inappropriate prescribing of glucose-lowering agents for renal impairment patients [330] and identifying prescriptions with drug-drug interactions [331]. The safety information about gabapentinoids generated in this project could be implemented into CDSS with appropriate alerting thresholds (i.e. sensitivity) and content to inform the risks of prescribing gabapentinoids [332].

10.4.2. Implications for drug policy

Responsible prescribing of gabapentinoids

The gabapentinoid classification policy comes from one of the four strategies stated in the 2017 Drug Strategy by the UK Home Office to tackle drug misuse and the harm it causes [333]. This project found that the April 2019 gabapentinoid classification did slow down the prescribing trend of gabapentinoids in English primary care. It is possible that the policy stopped some unnecessary gabapentinoid prescriptions and made the initiation of gabapentinoids more cautious and reasonable by making clinicians more responsible for gabapentinoid prescribing. Although the impact of the classification on reported gabapentinoid misuse and abuse cases had not been studied, the more complicated drug access process and more cautious prescribing led by the national policy should have already benefited the safety of gabapentinoids. However, national drug control policies are one-size-fits-all policies that often do not account for particular regional circumstances. As

found in Chapter 3, some geographical areas in England had a much higher prescribing rate of gabapentinoids and some practice-level patient characteristics were associated with prescribing gabapentinoids. Therefore, based on the findings in this project, it could be reasonable to establish regional prescribing policies for healthcare providers to reduce the misuse and abuse potential of gabapentinoids in local healthcare settings such as Integrated Care Systems.

Optimised chronic pain management

Limiting gabapentinoid prescription may reduce gabapentinoid misuse and abuse by reducing inappropriate prescriptions, but it does not tackle the problems that lead to gabapentinoid misuse. Patients sometimes self-medicate gabapentinoids because their expectations for pain management were not met [322], which could probably result in persistent and high-dose gabapentinoid use. Therefore, it is important to promote interdisciplinary pain management strategies, especially physical and psychological therapy, to optimise chronic pain management and reduce patients' dependence on drug therapy [5, 334]. Meanwhile, increasing the accessibility to pain specialist services could improve the efficiency of pain management.

Promotional campaigns for appropriate pain management and gabapentinoid safety awareness could also largely increase the safety of gabapentinoids. Since the concern for gabapentinoids' role in drug addiction and abuse was not widely discussed until the past decade, there have not been public campaigns about gabapentinoid safety. In contrast, campaigns about opioid safety in response to the opioid epidemic have been widely adopted in western countries and achieved good effects in reducing opioid harm [335, 336]. Frkovich *et al.* (2022) identified 166 online-accessible opioid-related campaigns in the US from July 2019 to June 2020 [335]. The study found the most common organisations leading the campaigns were

health service departments (54.8%) and the most frequent campaign topics were prevention and stigma [335]. Learning from the experience of opioid campaigns, it is recommended to run local or NHS-wide campaigns that implement the findings of this project as part of the evidence-based information to help prevent gabapentinoid-related safety issues, and include warnings about the long-term risk of serious adverse events and the short-term risk of fracture hospitalisations.

10.4.3. Implications for future studies

Research methods

This project applied a pharmacoepidemiological approach to investigate the safety issues relevant to gabapentinoids in English primary care. The drug utilisation results generated in this project were based on the prescription records in drug dispensing databases or EMRs, which may not reflect the actual use of the prescribed drugs in patients. As the risk of gabapentinoids was particularly high in high-dose users, it is important to understand the full profile of these people's gabapentinoid use including the way they consumed the prescribed gabapentinoids and any access they may have had to additional gabapentinoids and other illicit drugs outside primary care. On the other hand, drug use is not driven solely by medical factors; social factors such as patients' behavioural, psychological and social relationship details can also play a role [337]. A number of landmark qualitative studies have challenged the stereotypes (e.g. drug addiction was thought to be a pure pharmacological effect before *Zinberg* proposed the impact of psychology and social content in 1984 [338]) and provided the foundation for knowledge development in drug use in the past ninety years [337]. Therefore, qualitative studies that provide insights into patients' gabapentinoid use experiences are recommended for future research to understand and prevent harms relevant to gabapentinoids [339].

Study outcomes

This project focused on the association between gabapentinoid utilisation patterns and drug safety. It highlighted the potential risk of high dose and persistent gabapentinoid use and particularly studied the association between the time periods of gabapentinoid exposure and fracture hospitalisation risk. However, the risk of other drug utilisation patterns such as concurrent use with opioids has not been investigated in the UK. Therefore, further studies are recommended to explore other potentially risky utilisation patterns of gabapentinoids. The adverse events investigated in this project were limited to drug-related deaths, suicides and fracture hospitalisations based on the current case reports and pharmacological mechanisms of gabapentinoids. Other adverse events such as substance misuse and abuse [102, 160] could be investigated in future studies.

Moreover, the efficacy and safety of gabapentinoids in new emerging off-label use is another topic that needs researchers' attention. Chapter 9 found the potential of gabapentinoids being prescribed for fracture pain in secondary care, but whether this off-label use in fracture pain is common and whether the benefit outweighs the harm in this situation needs further study. Similarly, the off-label use of gabapentinoids for postoperative pain has increased due to the de-prescribing of opioids [340, 341]. Bongiovanni *et al.* (2022) studied gabapentinoid use after non-cataract surgical procedures among patients over 65 years in the Medicare database [342]. The study found more than 20% of the older adults who received post-operative gabapentinoids refilled a prescription more than 90 days after discharge, which could result in a higher risk of adverse events and polypharmacy [342]. Therefore, the efficacy of gabapentinoids on postoperative pain needs to be studied to justify these decisions.

Methodologies

Despite gabapentinoids being primarily used for chronic pain, the safety of gabapentinoids prescribed for other diseases still needs evaluation in future studies. Also, a single pharmacoepidemiological study question could be investigated using various study designs and statistical models, future studies are recommended to investigate the association between gabapentinoids and serious adverse events using different methods from this project to cross-validate the results. In addition, the confounders adjusted in this study were selected based on data availability in CPRD and the researcher's knowledge and judgement. Other confounders not included in this project could be tested in future studies to further establish the influential factors of prescribing gabapentinoids.

This study used the CPRD primary care database as the data source for gabapentinoid prescription in primary care. Future studies could use other UK regional or national primary care databases, registration data or special setting data (e.g. prison data) to cross-validate the results in this project and help identify potential sampling bias in this project. In addition, primary data collection such as interviews at pharmacy dispensing could also be applied to investigate specific gabapentinoid utilisation patterns.

A self-controlled case-series (SCCS) study design was adopted in this project to assess the risk of fracture hospitalisations at different time periods during gabapentinoid exposures. It overcomes many limitations of pharmacoepidemiological studies by using patients as their own control to adjust for non-time-varying confounders and enabling investigation of the temporal association between a time-varying exposure and an adverse event [292]. It was

first applied for vaccine safety and gradually used in pharmacoepidemiological studies. The use of the SCCS design is recommended for future pharmacoepidemiological studies that are prone to confounding bias and have temporal associations between exposures and outcomes.

10.5. Conclusion

This project evaluated the effectiveness of the gabapentinoid classification policy in limiting unnecessary gabapentinoid prescriptions in English primary care and identified the geographical variation in general practices prescribing gabapentinoids. The results suggested a plausible effect of national gabapentinoid policy that could be adopted regionally in the areas that were identified as “high-risk” areas to more precisely reduce gabapentinoid harm.

This project found that gabapentinoid use, especially some utilisation patterns, is not as safe as people normally thought. The initiation of gabapentinoids in patients with CNCP is associated with a higher risk of serious adverse events, where high-dose gabapentinoid use potentially built up from persistent use is particularly risky. A history of psychoactive substance misuse or alcohol use problem would also increase the risk of gabapentinoid-related serious adverse events. These findings informed clinicians about risk factors that need extra attention when prescribing gabapentinoids and facilitated the information input for CDSS. This project also highlighted the risk of fracture hospitalisations in the first two weeks of a gabapentinoid exposure, which emphasised the importance of dose titrating and fracture-preventing measures at the initiation of gabapentinoids. Further studies are suggested to explore more risky utilisation patterns and safety outcomes in gabapentinoids to help reduce harm.

References

1. R. D. Treede, W. Rief, A. Barke*, et al.*, *Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11).* Pain, 2019. **160**(1): p. 19-27.

2. A. M. Elliott, B. H. Smith, K. I. Penny*, et al.*, *The epidemiology of chronic pain in the community.* Lancet, 1999. **354**(9186): p. 1248-52.

3. A. Fayaz, P. Croft, R. M. Langford*, et al.*, *Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies.* BMJ Open, 2016. **6**(6): p. e010364.

4. S. P. Cohen, L. Vase, and W. M. Hooten, *Chronic pain: an update on burden, best practices, and new advances.* Lancet, 2021. **397**(10289): p. 2082-2097.

5. S. Carville, M. Constanti, N. Kosky*, et al.*, *Chronic pain (primary and secondary) in over 16s: summary of NICE guidance.* BMJ, 2021. **373**: p. n895.

6. F. Montastruc, S. Y. Loo, and C. Renoux, *Trends in first gabapentin and pregabalin prescriptions in primary care in the united kingdom, 1993-2017.* JAMA, 2018. **320**(20): p. 2149-2151.

7. H. N. Bockbrader, D. Wesche, R. Miller*, et al.*, *A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin.* Clinical Pharmacokinetics, 2010. **49**(10): p. 661-669.

8. Joint Formulary Committee, *British national formulary (BMJ Group and Pharmaceutical Press, London)*. 2020.

9. K. Green, N. Cooke O'Dowd, H. Watt*, et al.*, *Prescribing trends of gabapentin, pregabalin, and oxycodone: a secondary analysis of primary care prescribing patterns in England.* BJGP Open, 2019. **3**: p. 3.

10. E. E. Morrison, E. A. Sandilands, and D. J. Webb, *Gabapentin and pregabalin: do the benefits outweigh the harms?* J R Coll Physicians Edinb, 2017. **47**(4): p. 310-313.

11. D. Spence, *Bad medicine: gabapentin and pregabalin.* BMJ, 2013. **347**: p. f6747.

12. L. Iversen. *Advice on the anticonvulsant drugs Pregabalin and Gabapentin*. 2016 [cited 01 Feb 2019]; Available from: https://www.gov.uk/government/publications/advice-on-the-anticonvulsant-drugs-pregabalin-and-gabapentin.

13. G. Iacobucci, *UK government to reclassify pregabalin and gabapentin after rise in deaths.* BMJ, 2017. **358**: p. j4441.

14. Y. S. Althobaiti, A. Almalki, H. Alsaab*, et al.*, *Pregabalin: Potential for Addiction and a Possible Glutamatergic Mechanism.* Sci Rep, 2019. **9**(1): p. 15136.

15. Y. S. Althobaiti, A. Alghorabi, F. S. Alshehri*, et al.*, *Gabapentin-induced drug-seeking-like behavior: a potential role for the dopaminergic system.* Scientific Reports, 2020. **10**(1): p. 10445.

16. M. Chincholkar, *Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice.* Br J Pain, 2020. **14**(2): p. 104-114.

17. J. L. Montastruc, J. Benevent, F. Montastruc*, et al.*, *What is pharmacoepidemiology? Definition, methods, interest and clinical applications.* Therapie, 2019. **74**(2): p. 169-174.

18. L. H. Roht, B. J. Selwyn, and A. H. Holguin, *Principles of epidemiology: A self-teaching guide*. 2013: Elsevier.

19. R. D. Gibbons, K. Hur, C. H. Brown*, et al.*, *Gabapentin and suicide attempts.* Pharmacoepidemiol Drug Saf, 2010. **19**(12): p. 1241-7.

20. Y. Molero, H. Larsson, B. M. D'Onofrio*, et al.*, *Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden.* Bmj, 2019. **365**: p. l2147.

21. Y. Miyamoto, M. Iwagami, S. Aso*, et al.*, *Pregabalin and injury: A nested case-control and case-crossover study.* Pharmacoepidemiology and drug safety, 2020: p. 10.1002/pds.4976.

22. T. Gomes, S. Greaves, W. van den Brink*, et al.*, *Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study.* Ann Intern Med, 2018. **169**(10): p. 732-734.

23. T. Gomes, D. N. Juurlink, T. Antoniou*, et al.*, *Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study.* PLOS Medicine, 2017. **14**(10): p. e1002396.

24. S. E. E. Mills, K. P. Nicolson, and B. H. Smith, *Chronic pain: a review of its epidemiology and associated factors in population-based studies.* British journal of anaesthesia, 2019. **123**(2): p. e273-e283.

25. A. C. d. C. Williams and K. D. Craig, *Updating the definition of pain.* PAIN, 2016. **157**(11): p. 2420-2423.

26. C. J. Woolf, *What is this thing called pain?* J Clin Invest, 2010. **120**(11): p. 3742-4.

27. M. A. Fitzcharles, S. P. Cohen, D. J. Clauw*, et al.*, *Nociplastic pain: towards an understanding of prevalent pain conditions.* Lancet, 2021. **397**(10289): p. 2098-2110.

28. D. B. Carr and L. C. Goudas, *Acute pain.* The Lancet, 1999. **353**(9169): p. 2051-2058.

29. J. Scholz, *Mechanisms of chronic pain.* Molecular Pain, 2014. **10**(Suppl 1): p. O15-O15.

30. R.-D. Treede, W. Rief, A. Barke*, et al.*, *A classification of chronic pain for ICD-11.* Pain, 2015. **156**(6): p. 1003-1007.

31. R. M. Leadley, N. Armstrong, Y. C. Lee*, et al.*, *Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain.* J Pain Palliat Care Pharmacother, 2012. **26**(4): p. 310-25.

32. J. Dahlhamer, J. Lucas, C. Zelaya*, et al.*, *Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016.* MMWR Morb Mortal Wkly Rep, 2018. **67**(36): p. 1001-1006.

33. T. Jackson, S. Thomas, V. Stabile*, et al.*, *A Systematic Review and Meta-Analysis of the Global Burden of Chronic Pain Without Clear Etiology in Low- and Middle-Income Countries: Trends in Heterogeneous Data and a Proposal for New Assessment Methods.* Anesth Analg, 2016. **123**(3): p. 739-48.

34. D. Schopflocher, P. Taenzer, and R. Jovey, *The prevalence of chronic pain in Canada.* Pain research and management, 2011. **16**(6): p. 445-450.

35. A. Todd, N. Akhter, J.-M. Cairns*, et al.*, *The Pain Divide: a cross-sectional analysis of chronic pain prevalence, pain intensity and opioid utilisation in England.* BMJ Open, 2018. **8**(7).

36. C. J. Murray, C. Atkinson, K. Bhalla*, et al.*, *The state of US health, 1990-2010: burden of diseases, injuries, and risk factors.* Jama, 2013. **310**(6): p. 591-608.

37. J. Steglitz, J. Buscemi, and M. J. Ferguson, *The future of pain research, education, and treatment: a summary of the IOM report "Relieving pain in America: a blueprint*

for transforming prevention, care, education, and research". Transl Behav Med, 2012. **2**(1): p. 6-8.

38. J. Rivera, J. Rejas, J. Esteve-Vives*, et al.*, *Resource utilisation and health care costs in patients diagnosed with fibromyalgia in Spain.* Clin Exp Rheumatol, 2009. **27**(5 Suppl 56): p. S39-45.

39. C. M. Wenig, C. O. Schmidt, T. Kohlmann*, et al.*, *Costs of back pain in Germany.* Eur J Pain, 2009. **13**(3): p. 280-6.

40. Editorial, *Rethinking chronic pain.* Lancet, 2021. **397**(10289): p. 2023.

41. J. Kowal, K. G. Wilson, L. A. McWilliams*, et al.*, *Self-perceived burden in chronic pain: relevance, prevalence, and predictors.* Pain, 2012. **153**(8): p. 1735-41.

42. J. M. Hooley, J. C. Franklin, and M. K. Nock, *Chronic pain and suicide: understanding the association.* Curr Pain Headache Rep, 2014. **18**(8): p. 435.

43. M. M. Gerrits, P. van Oppen, H. W. van Marwijk*, et al.*, *Pain and the onset of depressive and anxiety disorders.* Pain, 2014. **155**(1): p. 53-9.

44. National Institute for Health and Care Excellence. *Neuropathic pain in adults: pharmacological management in non-specialist settings*. [NICE Guidance] 2019 [cited 01 February 2019]; Available from: https://www.nice.org.uk/guidance/cg173.

45. Scottish Intercollegiate Guidelines Network. *Management of chronic pain*. 2013 [cited 01 February 2019]; Available from: https://www.sign.ac.uk/sign-136-management-of-chronic-pain.

46. A. Gamsa, *The role of psychological factors in chronic pain. I. A half century of study.* Pain, 1994. **57**(1): p. 5-15.

47. R. D. Kerns, J. Sellinger, and B. R. Goodin, *Psychological Treatment of Chronic Pain.* Annual Review of Clinical Psychology, 2011. **7**(1): p. 411-434.

48. A. C. d. C. Williams, C. Eccleston, and S. Morley *Psychological therapies for the management of chronic pain (excluding headache) in adults*. The Cochrane database of systematic reviews, 2012. **11**, CD007407 DOI: 10.1002/14651858.cd007407.pub3.

49. D. C. Turk, H. D. Wilson, and A. Cahana, *Treatment of chronic non-cancer pain.* The Lancet, 2011. **377**(9784): p. 2226-2235.

50. World Health Organization. *WHO's cancer pain ladder for adults*. [cited 25 November 2018]; Available from: http://www.who.int/cancer/palliative/painladder/en/.

51. D. Dowell, T. M. Haegerich, and R. Chou, *CDC guideline for prescribing opioids for chronic pain—United States, 2016.* Jama, 2016. **315**(15): p. 1624-1645.

52. J. C. Ballantyne and N. S. Shin, *Efficacy of opioids for chronic pain: a review of the evidence.* The Clinical journal of pain, 2008. **24**(6): p. 469-478.

53. E. Kalso, J. E. Edwards, R. A. Moore*, et al.*, *Opioids in chronic non-cancer pain: systematic review of efficacy and safety.* Pain, 2004. **112**(3): p. 372-380.

54. J. C. Ballantyne and J. Mao, *Opioid therapy for chronic pain.* New England Journal of Medicine, 2003. **349**(20): p. 1943-1953.

55. K. M. Dunn, K. W. Saunders, C. M. Rutter*, et al.*, *Opioid prescriptions for chronic pain and overdose: a cohort study.* Annals of internal medicine, 2010. **152**(2): p. 85-92.

56. J. Højsted and P. Sjøgren, *Addiction to opioids in chronic pain patients: a literature review.* European Journal of Pain, 2007. **11**(5): p. 490-518.

57. N. Vadivelu, R. D. Urman, and R. L. Hines, *Essentials of pain management*. Vol. 337. 2011, New York: Springer.

58. W. T. Enthoven, P. D. Roelofs, R. A. Deyo*, et al.*, *Non-steroidal anti-inflammatory drugs for chronic low back pain.* Cochrane Database Syst Rev, 2016. **2**: p. Cd012087.

59. J. M. Bjordal, A. E. Ljunggren, A. Klovning*, et al.*, *Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials.* BMJ, 2004. **329**(7478): p. 1317.

60. T. Vo, A. S. Rice, and R. H. Dworkin, *Non-steroidal anti-inflammatory drugs for neuropathic pain: how do we explain continued widespread use?* Pain, 2009. **143**(3): p. 169-71.

61. Z. N. Ennis, D. Dideriksen, H. B. Vaegter*, et al.*, *Acetaminophen for Chronic Pain: A Systematic Review on Efficacy.* Basic Clin Pharmacol Toxicol, 2016. **118**(3): p. 184-9.

62. T. E. Towheed, L. Maxwell, M. G. Judd*, et al.*, *Acetaminophen for osteoarthritis.* Cochrane Database Syst Rev, 2006. **2006**(1): p. Cd004257.

63. H. R. Khouzam, *Psychopharmacology of chronic pain: a focus on antidepressants and atypical antipsychotics.* Postgrad Med, 2016. **128**(3): p. 323-30.

64. B. Verdu, I. Decosterd, T. Buclin*, et al.*, *Antidepressants for the treatment of chronic pain.* Drugs, 2008. **68**(18): p. 2611-32.

65. P. J. Wiffen, S. Collins, H. J. McQuay*, et al.*, *Anticonvulsant drugs for acute and chronic pain.* Cochrane Database of Systematic Reviews, 2005(3).

66. I. W. Tremont-Lukats, C. Megeff, and M. M. Backonja, *Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy.* Drugs, 2000. **60**(5): p. 1029-52.

67. J. V. Pergolizzi and J. A. LeQuang, *Reappraising the use of benzodiazepines in chronic pain patients.* Postgrad Med, 2020. **132**(sup3): p. 10-12.

68. J. L. Cunningham, J. R. Craner, M. M. Evans*, et al.*, *Benzodiazepine use in patients with chronic pain in an interdisciplinary pain rehabilitation program.* J Pain Res, 2017. **10**: p. 311-317.

69. C. E. Argoff, *Topical analgesics in the management of acute and chronic pain.* Mayo Clin Proc, 2013. **88**(2): p. 195-205.

70. R. Patel and A. H. Dickenson, *Mechanisms of the gabapentinoids and α2δ-1 calcium channel subunit in neuropathic pain.* Pharmacology Research & Perspectives, 2016. **4**(2): p. e00205.

71. G. J. Sills, *The mechanisms of action of gabapentin and pregabalin.* Current Opinion in Pharmacology, 2006. **6**(1): p. 108-113.

72. P. Wilson, P. Watson, J. Haythornwaite*, et al.*, *Clinical pain management: Chronic pain*. 2nd ed. 2008, London: CPC Press.

73. C. W. Goodman and A. S. Brett, *Gabapentin and Pregabalin for Pain - Is Increased Prescribing a Cause for Concern?* N Engl J Med, 2017. **377**(5): p. 411-414.

74. Joint Formulary Committee, *BNF 76 (British National Formulary) September 2018*. 2018: Pharmaceutical Press.

75. J. D. Wallach and J. S. Ross, *Gabapentin approvals, off-label use, and lessons for postmarketing evaluation efforts.* JAMA, 2018. **319**(8): p. 776-778.

76. T. M. Wensel, K. W. Powe, and M. E. Cates, *Pregabalin for the Treatment of Generalized Anxiety Disorder.* Annals of Pharmacotherapy, 2012. **46**(3): p. 424-429.

77. A. Mack, *Examination of the evidence for off-label use of gabapentin.* Journal of Managed Care Pharmacy, 2003. **9**(6): p. 559-568.

78. C. A. Federico, T. Wang, A. Doussau*, et al.*, *Assessment of pregabalin postapproval trials and the suggestion of efficacy for new indications: A systematic review.* JAMA Internal Medicine, 2018. **179**(1): p. 90-97.

79. P. J. Wiffen, S. Derry, R. F. Bell*, et al.*, *Gabapentin for chronic neuropathic pain in adults.* Cochrane Database of Systematic Reviews, 2017(6).

80. T. E. Cooper, S. Derry, P. J. Wiffen*, et al.*, *Gabapentin for fibromyalgia pain in adults.* Cochrane Database of Systematic Reviews, 2017(1).

81. S. Derry, R. F. Bell, S. Straube*, et al.*, *Pregabalin for neuropathic pain in adults.* Cochrane Database of Systematic Reviews, 2019(1).

82. S. Derry, M. Cording, P. J. Wiffen*, et al.*, *Pregabalin for pain in fibromyalgia in adults.* Cochrane Database of Systematic Reviews, 2016(9).

83. K. S. Gurusamy, C. Lusuku, and B. R. Davidson, *Pregabalin for decreasing pancreatic pain in chronic pancreatitis.* Cochrane Database of Systematic Reviews, 2016(2).

84. S. Mathieson, C. G. Maher, A. J. McLachlan*, et al.*, *Trial of Pregabalin for Acute and Chronic Sciatica.* New England Journal of Medicine, 2017. **376**(12): p. 1111-1120.

85. H. Shanthanna, I. Gilron, M. Rajarathinam*, et al.*, *Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials.* PLoS Med, 2017. **14**(8): p. e1002369.

86. N. Attal and M. Barrot, *Is Pregabalin Ineffective in Acute or Chronic Sciatica?* N Engl J Med, 2017. **376**(12): p. 1169-1170.

87. T. Appleyard, J. Ashworth, J. Bedson*, et al.*, *Trends in gabapentinoid prescribing in patients with osteoarthritis: a United Kingdom national cohort study in primary care.* Osteoarthritis Cartilage, 2019. **27**(10): p. 1437-1444.

88. N. Torrance, A. Veluchamy, Y. Zhou*, et al.*, *Trends in gabapentinoid prescribing, co-prescribing of opioids and benzodiazepines, and associated deaths in Scotland.* Br J Anaesth, 2020. **125**(2): p. 159-167.

89. K. Asomaning, S. Abramsky, Q. Liu*, et al.*, *Pregabalin prescriptions in the United Kingdom: a drug utilisation study of The Health Improvement Network (THIN)*

primary care database. International Journal of Clinical Practice, 2016. **70**(5): p. 380-388.

90. The Pharmaceutical Benefits Scheme. *Expenditure and Prescriptions twelve months to 30 June 2018*. 2018 [cited 21 June 2019]; Available from: http://www.pbs.gov.au/info/statistics/expenditure-prescriptions/expenditure-prescriptions-twelve-months-to-30-june-2018.

91. M. Hirakata, S. Yoshida, S. Tanaka-Mizuno*, et al.*, *Pregabalin Prescription for Neuropathic Pain and Fibromyalgia: A Descriptive Study Using Administrative Database in Japan.* Pain Res Manag, 2018. **2018**: p. 2786151.

92. M. E. Johansen, *Gabapentinoid use in the united states 2002 through 2015.* JAMA Internal Medicine, 2018. **178**(2): p. 292-294.

93. S. C. Kim, J. E. Landon, and D. H. Solomon, *Clinical characteristics and medication uses among fibromyalgia patients newly prescribed amitriptyline, duloxetine, gabapentin, or pregabalin.* Arthritis Care Res (Hoboken), 2013. **65**(11): p. 1813-9.

94. M. Akazawa, W. Mimura, K. Togo*, et al.*, *Patterns of drug treatment in patients with osteoarthritis and chronic low back pain in Japan: a retrospective database study.* J Pain Res, 2019. **12**: p. 1631-1648.

95. Drug Enforcement Administration Department of Justice, *Schedules of controlled substances: placement of pregabalin into schedule V. Final rule.* Fed Regist, 2005. **70**(144): p. 43633-5.

96. A. M. Peckham, M. J. Ananickal, and D. A. Sclar, *Gabapentin use, abuse, and the US opioid epidemic: the case for reclassification as a controlled substance and the need for pharmacovigilance.* Risk Manag Healthc Policy, 2018. **11**: p. 109-116.

97. H. Kwok, W. Khuu, K. Fernandes*, et al.*, *Impact of Unrestricted Access to Pregabalin on the Use of Opioids and Other CNS-Active Medications: A Cross-Sectional Time Series Analysis.* Pain Med, 2017. **18**(6): p. 1019-1026.

98. L. V. Wilton and S. Shakir, *A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England.* Epilepsia, 2002. **43**(9): p. 983-92.

99. H. H. Cheng, W. C. Huang, and S. Y. Jeng, *Anti-epileptic drugs associated with fractures in the elderly: a preliminary population-based study.* Curr Med Res Opin, 2019. **35**(5): p. 903-907.

100. R. A. Moore, S. Straube, P. J. Wiffen*, et al.*, *Pregabalin for acute and chronic pain in adults.* Cochrane Database Syst Rev, 2009(3): p. Cd007076.

101. C. T. Rentsch, K. L. Morford, D. A. Fiellin*, et al.*, *Safety of Gabapentin Prescribed for Any Indication in a Large Clinical Cohort of 571,718 US Veterans with and without Alcohol Use Disorder.* Alcohol Clin Exp Res, 2020.

102. K. E. Evoy, M. D. Morrison, and S. R. Saklad, *Abuse and Misuse of Pregabalin and Gabapentin.* Drugs, 2017. **77**(4): p. 403-426.

103. S. Lottner-Nau, B. Övgüer, L. D. Paul*, et al.*, *Abuse of pregabalin–results of the postmortem toxicology from 2010 to 2012.* Toxichem Krimtech, 2013. **80**(special issue): p. 339-342.

104. M. Hakkinen, E. Vuori, E. Kalso*, et al.*, *Profiles of pregabalin and gabapentin abuse by postmortem toxicology.* Forensic Sci Int, 2014. **241**: p. 1-6.

105. J. A. Eastwood and E. Davison, *Pregabalin concentrations in post-mortem blood-A two year study.* Forensic Sci Int, 2016. **266**: p. 197-201.

106. Office for National Statistics. *Number of drug-related deaths involving Gabapentin or Pregabalin with or without an opioid drug, England and Wales, 2018*. 2018 [cited 05 December 2019]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/10713numberofdrugrelateddeathsinvolvinggabapentinorpregabalinwithorwithoutanopioiddrugenglandandwales2018.

107. L. K. Nahar, K. G. Murphy, and S. Paterson, *Misuse and Mortality Related to Gabapentin and Pregabalin are Being Under-Estimated: A Two-Year Post-Mortem Population Study.* J Anal Toxicol, 2019. **43**(7): p. 564-570.

108. N. J. Kalk, C.-T. Chiu, R. Sadoughi*, et al.*, *Fatalities associated with gabapentinoids in England (2004–2020).* British Journal of Clinical Pharmacology, 2022. **88**(8): p. 3911-3917.

109. T. Abrahamsson, J. Berge, A. Ojehagen*, et al.*, *Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment-A nation-wide register-based open cohort study.* Drug Alcohol Depend, 2017. **174**: p. 58-64.

110. U.S. Department of Health and Human Services. *Antiepileptic drugs and suicidality*. STATISTICAL REVIEW AND EVALUATION 2008 [cited 05 Jun 2022]; Available from: https://www.fda.gov/files/drugs/published/Statistical-Review-and-Evaluation--Antiepileptic-Drugs-and-Suicidality.pdf.

111. E. Patorno, R. L. Bohn, P. M. Wahl*, et al.*, *Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death.* JAMA, 2010. **303**(14): p. 1401-1409.

112. F. Schifano, *Misuse and abuse of pregabalin and gabapentin: cause for concern?* CNS Drugs, 2014. **28**(6): p. 491-6.

113. V. Kapil, J. L. Green, M.-C. Le Lait*, et al.*, *Misuse of the γ-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK.* British Journal of Clinical Pharmacology, 2014. **78**(1): p. 190-191.

114. J. B. Bossard, C. Ponte, J. Dupouy*, et al.*, *Disproportionality Analysis for the Assessment of Abuse and Dependence Potential of Pregabalin in the French Pharmacovigilance Database.* Clin Drug Investig, 2016. **36**(9): p. 735-742.

115. S. Chiappini and F. Schifano, *A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database.* CNS Drugs, 2016. **30**(7): p. 647-654.

116. M. Gahr, R. W. Freudenmann, C. Hiemke*, et al.*, *Pregabalin abuse and dependence in Germany: results from a database query.* Eur J Clin Pharmacol, 2013. **69**(6): p. 1335-42.

117. J. P. Zacny, J. A. Paice, and D. W. Coalson, *Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers.* Pharmacol Biochem Behav, 2012. **100**(3): p. 560-5.

118. B. H. Smith, C. Higgins, A. Baldacchino*, et al.*, *Substance misuse of gabapentin.* British Journal of General Practice, 2012. **62**(601): p. 406-407.

119. F. Schifano, S. D'Offizi, M. Piccione*, et al.*, *Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data.* Psychother Psychosom, 2011. **80**(2): p. 118-22.

120. B. Jonsson, E. Backman, H. Salmonson*, et al.*, *Injection of crushed tablets--a prospective observational study.* Clin Toxicol (Phila), 2014. **52**(9): p. 982-3.

121. C. R. Baird, P. Fox, and L. A. Colvin, *Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers.* Eur Addict Res, 2014. **20**(3): p. 115-8.

122. L. Bastiaens, J. Galus, and C. Mazur, *Abuse of Gabapentin is Associated with Opioid Addiction.* Psychiatric Quarterly, 2016. **87**(4): p. 763-767.

123. T. Wilens, C. Zulauf, D. Ryland*, et al.*, *Prescription medication misuse among opioid dependent patients seeking inpatient detoxification.* Am J Addict, 2015. **24**(2): p. 173-7.

124. M. Grosshans, T. Lemenager, C. Vollmert*, et al.*, *Pregabalin abuse among opiate addicted patients.* Eur J Clin Pharmacol, 2013. **69**(12): p. 2021-5.

125. R. V. Smith, M. R. Lofwall, and J. R. Havens, *Abuse and diversion of gabapentin among nonmedical prescription opioid users in Appalachian Kentucky.* Am J Psychiatry, 2015. **172**(5): p. 487-8.

126. A. M. Peckham, K. A. Fairman, and D. A. Sclar, *Call for increased pharmacovigilance of gabapentin.* BMJ, 2017. **359**: p. j5456.

127. Office for National Statistics. *Deaths related to drug poisoning in England and Wales: 2017 registrations*. 2017 [cited 01 March 2019]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2017registrations.

128. E. A. Shipton, E. E. Shipton, and A. J. Shipton, *A Review of the Opioid Epidemic: What Do We Do About It?* Pain and therapy, 2018. **7**(1): p. 23-36.

129. R. Boden, B. Wettermark, L. Brandt*, et al.*, *Factors associated with pregabalin dispensing at higher than the approved maximum dose.* Eur J Clin Pharmacol, 2014. **70**(2): p. 197-204.

130. P. Braveman and L. Gottlieb, *The social determinants of health: it's time to consider the causes of the causes.* Public Health Reports, 2014. **129 Suppl 2**: p. 19-31.

131. J. B. Beuscart, M. Genin, C. Dupont*, et al.*, *Potentially inappropriate medication prescribing is associated with socioeconomic factors: a spatial analysis in the French Nord-Pas-de-Calais Region.* Age and Ageing, 2017. **46**(4): p. 607-613.

132. H. J. Curtis, R. Croker, A. J. Walker*, et al.*, *Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study.* The Lancet Psychiatry, 2019. **6**(2): p. 140-150.

133. V. A. Pear, W. R. Ponicki, A. Gaidus*, et al.*, *Urban-rural variation in the socioeconomic determinants of opioid overdose.* Drug and alcohol dependence, 2019. **195**: p. 66-73.

134. T.-C. Chen, L.-C. Chen, M. Kerry*, et al.*, *Prescription opioids: Regional variation and socioeconomic status – evidence from primary care in England.* International Journal of Drug Policy, 2019. **64**: p. 87-94.

135. Ministry of Housing Communities and Local Government, *The English Indices of Deprivation 2019*. 2019.

136. H. J. Curtis, A. J. Walker, K. R. Mahtani*, et al.*, *Time trends and geographical variation in prescribing of antibiotics in England 1998-2017.* Journal of Antimicrobial Chemotherapy, 2019. **74**(1): p. 242-250.

137. NHS Digital. *Practice Level Prescribing Data*. [cited 01 March 2019]; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/practice-level-prescribing-data.

138. NHS Digital. *Patients Registered at a GP Practice*. 2021 [cited 09 November 2021]; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/patients-registered-at-a-gp-practice.

139. NHS Digital. *QOF 2018/19 results*. [cited 01 March 2019]; Available from: https://qof.digital.nhs.uk/.

140. NHS Digital. *About NHS Digital*. [cited 01 March 2019]; Available from: https://digital.nhs.uk/about-nhs-digital.

141. Office for National Statistics. *England population mid-year estimate*. 2019 [cited 01 March 2019]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/enpop/pop.

142. UK Data Service. *English Counties, 2011*. 2011 [cited 01 April 2019]; Available from: https://borders.ukdataservice.ac.uk/easy_download_data.html?data=England_ct_2011.

143. NHS BSA. *English Prescribing Dataset (EPD)*. [cited 09 November 2021]; Available from: https://opendata.nhsbsa.net/dataset/english-prescribing-data-epd.

144. World Health Organization. *Defined Daily Dose (DDD)*. Essential medicines and health products [cited 22 July 2019]; Available from: https://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/.

145. WHO Collaborating Centre for Drug Statistics Methodology. *ATC/DDD Index 2019*. 2019 [cited 05 August 2019]; Available from: https://www.whocc.no/atc_ddd_index/.

146. Ministry of Housing Communities and Local Government. *English indices of deprivation 2019 Postcode Lookup tool*. 2019 [cited 12 December 2019]; Available from: http://imd-by-postcode.opendatacommunities.org/imd/2019.

147. National Health Services. *How to register with a GP surgery*. [cited 15 December 2022]; Available from: https://www.nhs.uk/nhs-services/gps/how-to-register-with-a-gp-surgery/.

148. D. S. Nagin, *Group-based trajectory modeling: an overview.* Ann Nutr Metab, 2014. **65**(2-3): p. 205-10.

149. D. S. Nagin and D. NAGIN, *Group-based modeling of development*. 2005: Harvard University Press.

150. D. S. Nagin and C. L. Odgers, *Group-based trajectory modeling in clinical research.* Annu Rev Clin Psychol, 2010. **6**: p. 109-38.

151. B. W. Silverman, *A Fast and Efficient Cross-Validation Method for Smoothing Parameter Choice in Spline Regression.* Journal of the American Statistical Association, 1984. **79**(387): p. 584-589.

152. C. Duncan, K. Jones, and G. Moon, *Context, composition and heterogeneity: using multilevel models in health research.* Soc Sci Med, 1998. **46**(1): p. 97-117.

153. T. A. B. Snijders, *Multilevel Analysis*, in *International Encyclopedia of Statistical Science*, M. Lovric, Editor. 2011, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 879-882.

154. P. Boedeker, *Hierarchical linear modeling with maximum likelihood, restricted maximum likelihood, and fully Bayesian estimation.* Practical Assessment, Research and Evaluation, 2017. **22**(2): p. 2.

155. M. Marmot, *Health equity in England: the Marmot review 10 years on.* Bmj, 2020. **368**: p. m693.

156. M. R. Janevic, S. J. McLaughlin, A. A. Heapy*, et al.*, *Racial and Socioeconomic Disparities in Disabling Chronic Pain: Findings From the Health and Retirement Study.* The Journal of Pain, 2017. **18**(12): p. 1459-1467.

157. Office for National Statistics. *More than half of heroin/morphine misuse death hotspots in England and Wales are seaside locations*. 2018 [cited 01 February 2019]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/d

eaths/halfofheroinmorphinemisusedeathhotspotsinenglandandwalesareseasidelocations/2018-04-04.

158. S. V. Pasricha, M. Tadrous, W. Khuu*, et al.*, *Clinical indications associated with opioid initiation for pain management in Ontario, Canada: a population-based cohort study.* Pain, 2018. **159**(8): p. 1562-1568.

159. T. Appleyard, J. Ashworth, J. Bedson*, et al.*, *Trends in gabapentinoid prescribing in patients with osteoarthritis: a United Kingdom national cohort study in primary care.* Osteoarthritis and cartilage, 2019. **27**(10): p. 1437-1444.

160. U. Bonnet and N. Scherbaum, *How addictive are gabapentin and pregabalin? A systematic review.* European neuropsychopharmacology, 2017. **27**(12): p. 1185-1215.

161. Home Office and Victoria Atkins MP. *Pregabalin and gabapentin to be controlled as class C drugs*. 2018 [cited 03 December 2019]; Available from: https://www.gov.uk/government/news/pregabalin-and-gabapentin-to-be-controlled-as-class-c-drugs.

162. I. Torjesen, *Pregabalin and gabapentin: what impact will reclassification have on doctors and patients?* BMJ, 2019. **364**: p. l1107.

163. C. C. Topriceanu, A. Wong, J. C. Moon*, et al.*, *Evaluating access to health and care services during lockdown by the COVID-19 survey in five UK national longitudinal studies.* BMJ Open, 2021. **11**(3): p. e045813.

164. W. Malcolm, R. A. Seaton, G. Haddock*, et al.*, *Impact of the COVID-19 pandemic on community antibiotic prescribing in Scotland.* JAC Antimicrob Resist, 2020. **2**(4): p. dlaa105.

165. C. V. Chalitsios, T. M. McKeever, T. E. Langley*, et al.*, *Impact of COVID-19 on corticosteroids and antibiotics prescribing in England: an interrupted time series analysis.* Journal of Public Health, 2021. **43**(3): p. 517-520.

166. A. Z. Hussain, V. Paudyal, and M. A. Hadi, *Impact of the COVID-19 Pandemic on the Prescribing Patterns of First-Line Antibiotics in English Primary Care: A Longitudinal Analysis of National Prescribing Dataset.* Antibiotics (Basel), 2021. **10**(5).

167. M. J. Carr, A. K. Wright, L. Leelarathna*, et al.*, *Impact of COVID-19 restrictions on diabetes health checks and prescribing for people with type 2 diabetes: a UK-wide*

cohort study involving 618 161 people in primary care. BMJ Qual Saf, 2022. **31**(7): p. 503-514.

168. N. Attal, G. Cruccu, R. a. Baron*, et al.*, *EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision.* European journal of neurology, 2010. **17**(9): p. 1113-e88.

169. M. J. Bair, R. L. Robinson, W. Katon*, et al.*, *Depression and Pain Comorbidity: A Literature Review.* Archives of Internal Medicine, 2003. **163**(20): p. 2433-2445.

170. E. Patetsos and E. Horjales-Araujo, *Treating Chronic Pain with SSRIs: What Do We Know?* Pain Res Manag, 2016. **2016**.

171. M. Kremer, E. Salvat, A. Muller*, et al.*, *Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights.* Neuroscience, 2016. **338**: p. 183-206.

172. A. K. Wagner, S. B. Soumerai, F. Zhang*, et al.*, *Segmented regression analysis of interrupted time series studies in medication use research.* J Clin Pharm Ther, 2002. **27**(4): p. 299-309.

173. L. Bravo, J. A. Mico, and E. Berrocoso, *Discovery and development of tramadol for the treatment of pain.* Expert Opin Drug Discov, 2017. **12**(12): p. 1281-1291.

174. J. L. Bernal, S. Cummins, and A. Gasparrini, *Interrupted time series regression for the evaluation of public health interventions: a tutorial.* Int J Epidemiol, 2017. **46**(1): p. 348-355.

175. E. Kontopantelis, T. Doran, D. A. Springate*, et al.*, *Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis.* BMJ, 2015. **350**: p. h2750.

176. A. Linden, *Conducting Interrupted Time-series Analysis for Single- and Multiple-group Comparisons.* The Stata Journal, 2015. **15**(2): p. 480-500.

177. F. Zhang, A. K. Wagner, and D. Ross-Degnan, *Simulation-based power calculation for designing interrupted time series analyses of health policy interventions.* J Clin Epidemiol, 2011. **64**(11): p. 1252-61.

178. J. S. Frazer and G. R. Frazer, *Analysis of primary care prescription trends in England during the COVID-19 pandemic compared against a predictive model.* Fam Med Community Health, 2021. **9**(3): p. e001143.

179. J. Ashworth, R. Bajpai, S. Muller*, et al.*, *Trends in gabapentinoid prescribing in UK primary care using the Clinical Practice Research Datalink: an observational study.* The Lancet Regional Health – Europe, 2023. **27**: p. 100579.

180. G. Papazisis and D. Tzachanis, *Pregabalin's abuse potential: a mini review focusing on the pharmacological profile.* Int J Clin Pharmacol Ther, 2014. **52**(8): p. 709-16.

181. Office for National Statistics. *Deaths related to drug poisoning in England and Wales: 2021 registrations*. 2021 [cited 15 February 2023]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2021registrations.

182. E. Herrett, A. M. Gallagher, K. Bhaskaran*, et al.*, *Data Resource Profile: Clinical Practice Research Datalink (CPRD).* Int J Epidemiol, 2015. **44**(3): p. 827-36.

183. Z. Kmietowicz, *A century of general practice.* Bmj, 2006. **332**(7532): p. 39-40.

184. C. Price, W. Green, and O. Suhomlinova, *Twenty-five years of national health IT: exploring strategy, structure, and systems in the English NHS.* Journal of the American Medical Informatics Association, 2019. **26**(3): p. 188-197.

185. A. Wolf, D. Dedman, J. Campbell*, et al.*, *Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum.* Int J Epidemiol, 2019. **48**(6): p. 1740-1740g.

186. Clinical Practice Research Datalink. *Release Notes: CPRD GOLD September 2020*. 2020 [cited 17 September 2020]; Available from: https://www.cprd.com/data-highlights.

187. Cinical Practice Research Datalink. *Release Notes: CPRD Aurum September 2020*. 2020 [cited 17 September 2020]; Available from: https://www.cprd.com/data-highlights.

188. Clinical Practice Research Datalink. *CPRD Data: Primary care and linked data to address public health research*. 2020 [cited 10 April 2019]; Available from: https://www.cprd.com/Data.

189. NHS Digital. *Retirement of Read Version 2 and Clinical Terms Version 3*. 2020 [cited 26 September 2022]; Available from: https://digital.nhs.uk/services/terminology-and-classifications/read-codes#top.

190. NHS Digital. *SNOMED CT is a clinical vocabulary readable by computers*. 2022 [cited 26 September 2022]; Available from: https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct.

191. T. Smith, M. Noble, S. Noble*, et al.*, *The English Indices of Deprivation 2015*. 2015, Department for Communities and Local Government,: London.

192. NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18*. Hospital Admitted Patient Care Activity [cited 03 July 2019]; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18.

193. Clinical Practice Research Datalink. *Hospital Episode Statistics (HES) Admitted Patient Care and CPRD primary care data Documentation (Set 22/January 2022)*. 2022 [cited 30 September 2022]; Available from: https://cprd.com/cprd-linked-data#HES%20Admitted%20Patient%20Care%20data.

194. A. Boyd, R. Cornish, L. Johnson*, et al. Understanding Hospital Episode Statistics (HES)*. 2018 [cited; Available from: https://www.closer.ac.uk/wp-content/uploads/CLOSER-resource-Understanding-HES.pdf.

195. Office for National Statistics. *User guide to mortality statistics*. 2020 [cited 1 November 2020]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017#certification-of-cause-of-death.

196. Office for National Statistics. *Impact of registration delays on mortality statistics in England and Wales: 2020*. 2020 [cited 23 September 2020]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/impactofregistrationdelaysonmortalitystatisticsinenglandandwales/2020.

197. Clinical Practice Research Datalink. *ONS death registration data and CPRD primary care data Documentation (Set 17)*. 17 May 2019 [cited 03 July 2019]; Available from: https://cprd.eu/sites/default/files/ONS%20death%20registration%20data%20documentation.pdf.

198. O. A. Steingrimsdottir, T. Landmark, G. J. Macfarlane*, et al.*, *Defining chronic pain in epidemiological studies: a systematic review and meta-analysis.* Pain, 2017. **158**(11): p. 2092-2107.

199. D. A. Springate, E. Kontopantelis, D. M. Ashcroft*, et al.*, *ClinicalCodes: An Online Clinical Codes Repository to Improve the Validity and Reproducibility of Research Using Electronic Medical Records.* PLOS ONE, 2014. **9**(6): p. e99825.

200. A. Genova, O. Dix, M. Thakur*, et al.*, *Chronic Non-cancer Pain Management and Addiction: A Review.* Cureus, 2020. **12**(2): p. e6963.

201. T. Doran, E. Kontopantelis, J. M. Valderas*, et al.*, *Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework.* BMJ, 2011. **342**: p. d3590.

202. A. Nicholson, E. Ford, K. A. Davies*, et al.*, *Optimising Use of Electronic Health Records to Describe the Presentation of Rheumatoid Arthritis in Primary Care: A Strategy for Developing Code Lists.* PLOS ONE, 2013. **8**(2): p. e54878.

203. S. Reilly, I. Olier, C. Planner*, et al.*, *Inequalities in physical comorbidity: a longitudinal comparative cohort study of people with severe mental illness in the UK.* BMJ Open, 2015. **5**(12): p. e009010.

204. E. Kontopantelis, I. Olier, C. Planner*, et al.*, *Primary care consultation rates among people with and without severe mental illness: a UK cohort study using the Clinical Practice Research Datalink.* BMJ Open, 2015. **5**(12): p. e008650.

205. E. Kontopantelis, D. A. Springate, D. Reeves*, et al.*, *Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retrospective cohort study.* Diabetologia, 2015. **58**(3): p. 505-18.

206. H. C. Gorton, R. T. Webb, M. J. Carr*, et al.*, *Risk of Unnatural Mortality in People With Epilepsy.* JAMA Neurology, 2018. **75**(8): p. 929-938.

207. CPRD@Cambridge. *Codes Lists (GOLD)*. 2018 [cited 10 March 2022]; Available from: https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v11/.

208. London School of Hygiene & Tropical Medicine. *LSHTM Data Compass*. [cited 07 January 2023]; Available from: https://datacompass.lshtm.ac.uk/.

209. NHS Digital TRUD. *NHS Data Migration*. 2020 [cited 26 September 2022]; Available from: https://isd.digital.nhs.uk/trud/users/guest/filters/0/categories/9/items/9/releases.

210. E. Chang and J. Mostafa, *The use of SNOMED CT, 2013-2020: a literature review.* J Am Med Inform Assoc, 2021. **28**(9): p. 2017-2026.

211. N. Brusselaers and J. Lagergren, *The Charlson Comorbidity Index in Registry-based Research.* Methods Inf Med, 2017. **56**(5): p. 401-406.

212. N. F. Khan, R. Perera, S. Harper*, et al.*, *Adaptation and validation of the Charlson Index for Read/OXMIS coded databases.* BMC Fam Pract, 2010. **11**: p. 1.

213. Office for National Statistics. *Deaths related to drug poisoning in England and Wales QMI*. 2018 [cited 18 December 2019]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/deathsrelatedtodrugpoisoninginenglandandwalesqmi.

214. E. J. Peach, F. A. Pearce, J. Gibson*, et al.*, *Opioids and the Risk of Fracture: A Self-Controlled Case Series Study in the Clinical Practice Research Datalink.* Am J Epidemiol, 2021. **190**(7): p. 1324-1331.

215. National Institute of Mental Health. *Mental Health Information: Suicide*. [cited 20 April 2022]; Available from: https://www.nimh.nih.gov/health/statistics/suicide.

216. National Institute for Clinical Excellence. *Self-harm: assessment, management and preventing recurrence*. 2022 [cited 20 April 2022]; Available from: https://www.nice.org.uk/guidance/ng225.

217. H. Hedegaard, M. Schoenbaum, C. Claassen*, et al.*, *Issues in Developing a Surveillance Case Definition for Nonfatal Suicide Attempt and Intentional Self-harm Using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Coded Data.* Natl Health Stat Report, 2018(108): p. 1-19.

218. C. J. Mann, *Observational research methods. Research design II: cohort, cross sectional, and case-control studies.* Emergency Medicine Journal, 2003. **20**(1): p. 54-60.

219. R. Brazauskas and B. R. Logan, *Observational Studies: Matching or Regression?* Biol Blood Marrow Transplant, 2016. **22**(3): p. 557-63.

220. E. A. Stuart, *Matching methods for causal inference: A review and a look forward.* Stat Sci, 2010. **25**(1): p. 1-21.

221. M. Iwagami and T. Shinozaki, *Introduction to Matching in Case-Control and Cohort Studies.* Annals of Clinical Epidemiology, 2022. **4**(2): p. 33-40.

222. M. A. de Graaf, K. J. Jager, C. Zoccali*, et al.*, *Matching, an Appealing Method to Avoid Confounding?* Nephron Clinical Practice, 2011. **118**(4): p. c315-c318.

223. S. Evans, *Commentary: Matched cohorts can be useful.* Bmj, 2003. **326**(7385): p. 357.

224. J. Crush, N. Levy, R. D. Knaggs*, et al.*, *Misappropriation of the 1986 WHO analgesic ladder: the pitfalls of labelling opioids as weak or strong.* Br J Anaesth, 2022. **129**(2): p. 137-142.

225. G. Nahler and G. Nahler, *Anatomical therapeutic chemical classification system (ATC).* Dictionary of Pharmaceutical Medicine, 2009: p. 8-8.

226. M. Z. I. Chowdhury and T. C. Turin, *Variable selection strategies and its importance in clinical prediction modelling.* Fam Med Community Health, 2020. **8**(1): p. e000262.

227. N. J. Pauly, C. Delcher, S. Slavova*, et al.*, *Trends in Gabapentin Prescribing in a Commercially Insured U.S. Adult Population, 2009-2016.* J Manag Care Spec Pharm, 2020. **26**(3): p. 246-252.

228. R. Fuzier, I. Serres, E. Guitton*, et al.*, *Adverse drug reactions to gabapentin and pregabalin: a review of the French pharmacovigilance database.* Drug Saf, 2013. **36**(1): p. 55-62.

229. J. H. Scholl, R. van Eekeren, and E. P. van Puijenbroek, *Six cases of (severe) hypoglycaemia associated with gabapentin use in both diabetic and non-diabetic patients.* Br J Clin Pharmacol, 2015. **79**(5): p. 870-1.

230. R. Mukai, S. Hasegawa, R. Umetsu*, et al.*, *Evaluation of pregabalin-induced adverse events related to falls using the FDA adverse event reporting system and Japanese Adverse Drug Event Report databases.* J Clin Pharm Ther, 2019. **44**(2): p. 285-291.

231. A. M. Peckham, K. A. Fairman, and D. A. Sclar, *All-Cause and Drug-Related Medical Events Associated with Overuse of Gabapentin and/or Opioid Medications: A Retrospective Cohort Analysis of a Commercially Insured US Population.* Drug Saf, 2018. **41**(2): p. 213-228.

232. J. W. Song and K. C. Chung, *Observational studies: cohort and case-control studies.* Plastic and reconstructive surgery, 2010. **126**(6): p. 2234-2242.

233. N. M. Gajraj, *Pregabalin: its pharmacology and use in pain management.* Anesthesia & Analgesia, 2007. **105**(6): p. 1805-1815.

234. M. Rose and P. Kam, *Gabapentin: pharmacology and its use in pain management.* Anaesthesia, 2002. **57**(5): p. 451-462.

235. M. Naghavi, *Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016.* BMJ, 2019. **364**: p. l94.

236. GBD 2019 Fracture Collaborators, *Global, regional, and national burden of bone fractures in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019.* Lancet Healthy Longev, 2021. **2**(9): p. e580-e592.

237. A. M. Gallagher, D. Dedman, S. Padmanabhan*, et al.*, *The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations.* Pharmacoepidemiol Drug Saf, 2019. **28**(5): p. 563-569.

238. M. Beghi and J. F. Rosenbaum, *Risk factors for fatal and nonfatal repetition of suicide attempt: a critical appraisal.* 2010. **23**(4): p. 349-355.

239. D. Y. Dang, S. Zetumer, and A. L. Zhang, *Recurrent Fragility Fractures: A Cross-sectional Analysis.* JAAOS - Journal of the American Academy of Orthopaedic Surgeons, 2019. **27**(2).

240. T. J. VanderWeele, *Principles of confounder selection.* Eur J Epidemiol, 2019. **34**(3): p. 211-219.

241. F. Bailly and H. Belaid, *Suicidal ideation and suicide attempt associated with antidepressant and antiepileptic drugs: Implications for treatment of chronic pain.* Joint Bone Spine, 2020. **88**(1): p. 105005.

242. K. Hawton, I. C. C. Casanas, C. Haw*, et al.*, *Risk factors for suicide in individuals with depression: a systematic review.* J Affect Disord, 2013. **147**(1-3): p. 17-28.

243. T. P. van Staa, H. G. Leufkens, and C. Cooper, *Utility of medical and drug history in fracture risk prediction among men and women.* Bone, 2002. **31**(4): p. 508-14.

244. H. Sahai and A. Khurshid, *Confidence intervals for the mean of a Poisson distribution: a review.* Biometrical Journal, 1993. **35**(7): p. 857-867.

245. P. Schober and T. R. Vetter, *Survival Analysis and Interpretation of Time-to-Event Data: The Tortoise and the Hare.* Anesth Analg, 2018. **127**(3): p. 792-798.

246. T. G. Clark, M. J. Bradburn, S. B. Love*, et al.*, *Survival analysis part I: basic concepts and first analyses.* Br J Cancer, 2003. **89**(2): p. 232-8.

247. V. Bewick, L. Cheek, and J. Ball, *Statistics review 12: survival analysis.* Critical Care (London, England), 2004. **8**(5): p. 1-6.

248. J. M. Bland and D. G. Altman, *Survival probabilities (the Kaplan-Meier method).* BMJ, 1998. **317**(7172): p. 1572-1580.

249. B. George, S. Seals, and I. Aban, *Survival analysis and regression models.* J Nucl Cardiol, 2014. **21**(4): p. 686-94.

250. M. Noordzij, K. Leffondré, K. J. van Stralen*, et al.*, *When do we need competing risks methods for survival analysis in nephrology?* Nephrology Dialysis Transplantation, 2013. **28**(11): p. 2670-2677.

251. P. C. Austin, D. S. Lee, and J. P. Fine, *Introduction to the Analysis of Survival Data in the Presence of Competing Risks.* Circulation, 2016. **133**(6): p. 601-9.

252. P. Buzkova, *Competing risk of mortality in association studies of non-fatal events.* PLoS One, 2021. **16**(8): p. e0255313.

253. Office for National Statistics. *Suicides in England and Wales: 2021 registrations*. 2021 [cited 05 December 2022]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/suicidesintheunitedkingdom/2021registrations.

254. T. Jennison and M. Brinsden, *Fracture admission trends in England over a ten-year period.* Ann R Coll Surg Engl, 2019. **101**(3): p. 208-214.

255. N. Jetté, L. M. Lix, C. J. Metge*, et al.*, *Association of antiepileptic drugs with nontraumatic fractures: A population-based analysis.* Archives of Neurology, 2011. **68**(1): p. 107-112.

256. R. Shah, M. A. Raji, J. Westra*, et al.*, *Association of co-prescribing of opioid and benzodiazepine substitutes with incident falls and fractures among older adults: a cohort study.* BMJ Open, 2021. **11**(12): p. e052057.

257. S. Darke, J. Duflou, A. Peacock*, et al.*, *Characteristics of fatal gabapentinoid-related poisoning in Australia, 2000-2020.* Clin Toxicol (Phila), 2022. **60**(3): p. 304-310.

258. E. Lynn, G. Cousins, S. Lyons*, et al.*, *A repeated cross-sectional study of factors associated with pregabalin-positive poisoning deaths in Ireland.* Drug and Alcohol Dependence, 2020. **206**: p. 107741.

259. G. N. Pandey, *Biological basis of suicide and suicidal behavior.* Bipolar Disord, 2013. **15**(5): p. 524-41.

260. S. Gupta and P. Kulhara, *Cellular and molecular mechanisms of drug dependence: An overview and update.* Indian J Psychiatry, 2007. **49**(2): p. 85-90.

261. S. K. Gupta, *Intention-to-treat concept: A review.* Perspect Clin Res, 2011. **2**(3): p. 109-12.

262. E. B. Jorgensen, L. K. Overgaard, L. Folkestad*, et al.*, *The risk of fragility fractures following initiation of gabapentin and pregabalin-A Danish, nationwide, high-dimensional propensity score-matched cohort study.* Basic Clin Pharmacol Toxicol, 2023. **132**(5): p. 384-391.

263. E. O. Ogundimu, D. G. Altman, and G. S. Collins, *Adequate sample size for developing prediction models is not simply related to events per variable.* J Clin Epidemiol, 2016. **76**: p. 175-82.

264. A. Unnanuntana, B. P. Gladnick, E. Donnelly*, et al.*, *The assessment of fracture risk.* J Bone Joint Surg Am, 2010. **92**(3): p. 743-53.

265. A. L. Xue, S. Y. Wu, L. Jiang*, et al.*, *Bone fracture risk in patients with rheumatoid arthritis: A meta-analysis.* Medicine (Baltimore), 2017. **96**(36): p. e6983.

266. Z. Zhang, J. Reinikainen, K. A. Adeleke*, et al.*, *Time-varying covariates and coefficients in Cox regression models.* Ann Transl Med, 2018. **6**(7): p. 121.

267. F. T. Muanda, M. A. Weir, F. Ahmadi*, et al.*, *Higher-Dose Gabapentinoids and the Risk of Adverse Events in Older Adults With CKD: A Population-Based Cohort Study.* Am J Kidney Dis, 2022. **80**(1): p. 98-107.e1.

268. L. E. Levesque, J. A. Hanley, A. Kezouh*, et al.*, *Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes.* BMJ, 2010. **340**: p. b5087.

269. L. Rasmussen, B. Wettermark, D. Steinke*, et al.*, *Core concepts in pharmacoepidemiology: Measures of drug utilization based on individual-level drug dispensing data.* Pharmacoepidemiol Drug Saf, 2022. **31**(10): p. 1015-1026.

270. A. M. Tharp, K. Hobron, and T. Wright, *Gabapentin-related Deaths: Patterns of Abuse and Postmortem Levels.* J Forensic Sci, 2019. **64**(4): p. 1105-1111.

271. S. Slavova, A. Miller, T. L. Bunn*, et al.*, *Prevalence of gabapentin in drug overdose postmortem toxicology testing results.* Drug Alcohol Depend, 2018. **186**: p. 80-85.

272. L. Timmerman, D. L. Stronks, J. G. Groeneweg*, et al.*, *Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review.* Acta Anaesthesiologica Scandinavica, 2016. **60**(4): p. 416-431.

273. F. Bradley, R. Elvey, D. M. Ashcroft*, et al.*, *Influence of prescription charges on repeat prescribing in primary care.* Journal of Clinical Pharmacy and Therapeutics, 2007. **32**(3): p. 269-275.

274. K. M. Kennedy and J. O'Riordan, *Prescribing benzodiazepines in general practice.* Br J Gen Pract, 2019. **69**(680): p. 152-153.

275. C. A. Cadogan, C. Ryan, C. Cahir*, et al.*, *Benzodiazepine and Z-drug prescribing in Ireland: analysis of national prescribing trends from 2005 to 2015.* Br J Clin Pharmacol, 2018. **84**(6): p. 1354-1363.

276. D. Dowell, K. R. Ragan, C. M. Jones*, et al.*, *Prescribing Opioids for Pain - The New CDC Clinical Practice Guideline.* N Engl J Med, 2022. **387**(22): p. 2011-2013.

277. L. Rasmussen, N. Pratt, M. R. Hansen*, et al.*, *Using the "proportion of patients covered" and the Kaplan-Meier survival analysis to describe treatment persistence.* Pharmacoepidemiol Drug Saf, 2018. **27**(8): p. 867-871.

278. J. Hallas, H. Støvring, and A. Pottegård, *Individual‐level drug utilization analyses*, in *Drug Utilization Research: Methods and Applications*. 2016. p. 68-76.

279. O. Schjerning, A. Pottegård, P. Damkier*, et al.*, *Use of Pregabalin - A Nationwide Pharmacoepidemiological Drug Utilization Study with Focus on Abuse Potential.* Pharmacopsychiatry, 2016. **49**(4): p. 155-61.

280. A. Viniol, T. Ploner, L. Hickstein*, et al.*, *Prescribing practice of pregabalin/gabapentin in pain therapy: an evaluation of German claim data.* BMJ Open, 2019. **9**(3): p. e021535.

281. US Gabapentin Study Group, *The long-term safety and efficacy of gabapentin (Neurontin®) as add-on therapy in drug-resistant partial epilepsy.* Epilepsy Research, 1994. **18**(1): p. 67-73.

282. U. Bonnet, E. L. Richter, K. Isbruch*, et al.*, *On the addictive power of gabapentinoids: a mini-review.* Psychiatr Danub, 2018. **30**(2): p. 142-149.

283. Z. Zou, H. Wang, F. d'Oleire Uquillas*, et al.*, *Definition of Substance and Non-substance Addiction.* Adv Exp Med Biol, 2017. **1010**: p. 21-41.

284. M. Elseviers, B. Wettermark, A. B. Almarsdóttir*, et al.*, *Drug utilization research: methods and applications*. 1st ed. 2016, Chichester, West Sussex ;: John Wiley & Sons Inc.

285. D. Clark, M. Nakamura, T. Miclau*, et al.*, *Effects of Aging on Fracture Healing.* Curr Osteoporos Rep, 2017. **15**(6): p. 601-608.

286. A. Johansen, C. Grose, and W. Havelock, *Hip fractures in the winter - Using the National Hip Fracture Database to examine seasonal variation in incidence and mortality.* Injury, 2020. **51**(4): p. 1011-1014.

287. K. Donnelly, R. Bracchi, J. Hewitt*, et al.*, *Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis.* PLoS One, 2017. **12**(4): p. e0174730.

288. R. Tamblyn, D. W. Bates, D. L. Buckeridge*, et al.*, *Multinational Investigation of Fracture Risk with Antidepressant Use by Class, Drug, and Indication.* J Am Geriatr Soc, 2020. **68**(7): p. 1494-1503.

289. I. Petersen, I. Douglas, and H. Whitaker, *Self controlled case series methods: an alternative to standard epidemiological study designs.* BMJ, 2016. **354**: p. i4515.

290. J. Hallas and A. Pottegard, *Use of self-controlled designs in pharmacoepidemiology.* J Intern Med, 2014. **275**(6): p. 581-9.

291. T. A. Louis, P. W. Lavori, J. C. Bailar*, et al.*, *Crossover and self-controlled designs in clinical research.* N Engl J Med, 1984. **310**(1): p. 24-31.

292. H. J. Whitaker, M. N. Hocine, and C. P. Farrington, *The methodology of self-controlled case series studies.* Statistical Methods in Medical Research, 2009. **18**(1): p. 7-26.

293. T. V. Nguyen, J. R. Center, and J. A. Eisman, *Osteoporosis: underrated, underdiagnosed and undertreated.* Med J Aust, 2004. **180**(S5): p. S18-22.

294. S. Xu, C. Zeng, S. Newcomer*, et al.*, *Use of Fixed Effects Models to Analyze Self-Controlled Case Series Data in Vaccine Safety Studies.* J Biom Biostat, 2012. **Suppl 7**: p. 006.

295. F. Lewis, A. Butler, and L. Gilbert, *A unified approach to model selection using the likelihood ratio test.* Methods in Ecology and Evolution, 2011. **2**(2): p. 155-162.

296. Y. Miyamoto, M. Iwagami, S. Aso*, et al.*, *Pregabalin and injury: A nested case-control and case-crossover study.* Pharmacoepidemiol Drug Saf, 2020. **29**(5): p. 558-564.

297. National Institute for Health and Care Excellence. *Fractures (Complex): Assessment and Management*. 2016 [cited 02 Jan 2023]; Available from: https://www.nice.org.uk/guidance/ng37.

298. A. N. Kanani and S. Hartshorn, *NICE clinical guideline NG39: Major trauma: assessment and initial management.* Archives of Disease in Childhood-Education Practice Digest, 2017. **102**(1): p. 20-23.

299. S. A. T. Mitchell, L. A. Majuta, and P. W. Mantyh, *New Insights in Understanding and Treating Bone Fracture Pain.* Curr Osteoporos Rep, 2018. **16**(4): p. 325-332.

300. E. E. Moskowitz, L. Garabedian, K. Hardin*, et al.*, *A double-blind, randomized controlled trial of gabapentin vs. placebo for acute pain management in critically ill patients with rib fractures.* Injury, 2018. **49**(9): p. 1693-1698.

301. H. Y. Koo, E. B. Cho, S. H. Kong*, et al.*, *Fracture risk in Parkinson's disease according to its severity and duration.* Osteoporos Int, 2023. **34**(1): p. 81-89.

302. H. J. Whitaker, Y. Ghebremichael-Weldeselassie, I. J. Douglas*, et al.*, *Investigating the assumptions of the self-controlled case series method.* Stat Med, 2018. **37**(4): p. 643-658.

303. S. Mayor, *Pregabalin and gabapentin become controlled drugs to cut deaths from misuse.* BMJ, 2018. **363**: p. k4364.

304. UK Home Office. *Gabapentin (Neurontin): risk of severe respiratory depression*. Drug Safety Update 2017 [cited 22 September 2020]; Available from: https://www.gov.uk/drug-safety-update/gabapentin-neurontin-risk-of-severe-respiratory-depression.

305. A. Halaby, S. A. Kassm, and W. J. Naja, *Pregabalin dependence: a case report.* Curr Drug Saf, 2015. **10**(2): p. 184-6.

306. C. E. Hamm, R. D. Gary, and I. M. McIntyre, *Gabapentin concentrations and postmortem distribution.* Forensic Sci Int, 2016. **262**: p. 201-3.

307. H.-G. Eichler, F. Pignatti, B. Schwarzer-Daum*, et al.*, *Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth.* Clin Pharmacol Ther, 2021. **109**(5): p. 1212-1218.

308. A. Bérard, *Pharmacoepidemiology Research-Real-World Evidence for Decision Making.* Front Pharmacol, 2021. **12**: p. 723427.

309. R. Flynn, K. Plueschke, C. Quinten*, et al.*, *Marketing Authorization Applications Made to the European Medicines Agency in 2018-2019: What was the Contribution of Real-World Evidence?* Clin Pharmacol Ther, 2022. **111**(1): p. 90-97.

310. J. Wu, C. Wang, S. Toh*, et al.*, *Use of real-world evidence in regulatory decisions for rare diseases in the United States—Current status and future directions.* Pharmacoepidemiol Drug Saf, 2020. **29**(10): p. 1213-1218.

311. C. Lau, F. Jamali, and R. Loebenberg, *Health Canada Usage of Real World Evidence (RWE) in Regulatory Decision Making compared with FDA/EMA usage based on publicly available information.* J Pharm Pharm Sci, 2022. **25**: p. 227-236.

312. B. K. Beaulieu-Jones, S. G. Finlayson, W. Yuan*, et al.*, *Examining the Use of Real-World Evidence in the Regulatory Process.* Clin Pharmacol Ther, 2020. **107**(4): p. 843-852.

313. R. Silberzahn, E. L. Uhlmann, D. P. Martin*, et al.*, *Many Analysts, One Data Set: Making Transparent How Variations in Analytic Choices Affect Results.* Advances in Methods and Practices in Psychological Science, 2018. **1**(3): p. 337-356.

314. N. Moore, P. Blin, and C. Droz, *Pharmacoepidemiology.* Handb Exp Pharmacol, 2019. **260**: p. 433-451.

315. L. Timmerman, D. L. Stronks, J. G. Groeneweg*, et al.*, *Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review.* Acta Anaesthesiol Scand, 2016. **60**(4): p. 416-31.

316. L. C. Thygesen and A. K. Ersbøll, *When the entire population is the sample: strengths and limitations in register-based epidemiology.* European Journal of Epidemiology, 2014. **29**(8): p. 551-558.

317. V. Kapil, J. L. Green, M. C. Le Lait*, et al.*, *Misuse of the gamma-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK.* Br J Clin Pharmacol, 2014. **78**(1): p. 190-1.

318. A. Soni and P. Walters, *A study of the reasons for prescribing and misuse of gabapentinoids in prison including their co-prescription with opioids and antidepressants.* Int J Prison Health, 2019. **16**(1): p. 67-77.

319. S. Greenland and H. Morgenstern, *Matching and efficiency in cohort studies.* Am J Epidemiol, 1990. **131**(1): p. 151-9.

320. A. Sjölander and S. Greenland, *Ignoring the matching variables in cohort studies – when is it valid and why?* Stat Med, 2013. **32**(27): p. 4696-4708.

321. C. W. Goodman and A. S. Brett, *A Clinical Overview of Off-label Use of Gabapentinoid Drugs.* JAMA Intern Med, 2019. **179**(5): p. 695-701.

322. J. R. Covvey, M. L. Blakely, R. Singh*, et al.*, *Pharmacist, prescriber, and drug policy expert opinions on gabapentinoid misuse.* Res Social Adm Pharm, 2022.

323. J. Y. Yang, W. I. Lee, W. K. Shin*, et al.*, *Administration of four different doses of gabapentin reduces awakening from breakthrough pain and adverse effects in outpatients with neuropathic pain during the initial titration.* Korean J Anesthesiol, 2013. **65**(1): p. 48-54.

324. J. A. Kanis, N. C. Harvey, H. Johansson*, et al.*, *A decade of FRAX: how has it changed the management of osteoporosis?* Aging Clin Exp Res, 2020. **32**(2): p. 187-196.

325. M. K. Skjødt, S. Möller, N. Hyldig*, et al.*, *Validation of the Fracture Risk Evaluation Model (FREM) in predicting major osteoporotic fractures and hip fractures using administrative health data.* Bone, 2021. **147**: p. 115934.

326. K. H. Rubin, S. Möller, T. Holmberg*, et al.*, *A New Fracture Risk Assessment Tool (FREM) Based on Public Health Registries.* J Bone Miner Res, 2018. **33**(11): p. 1967-1979.

327. L. Dautzenberg, S. Beglinger, S. Tsokani*, et al.*, *Interventions for preventing falls and fall-related fractures in community-dwelling older adults: A systematic review and network meta-analysis.* J Am Geriatr Soc, 2021. **69**(10): p. 2973-2984.

328. C. Curtain, G. M. Peterson, P. Tenni*, et al.*, *Outcomes of a decision support prompt in community pharmacy-dispensing software to promote step-down of proton pump inhibitor therapy.* British Journal of Clinical Pharmacology, 2011. **71**(5): p. 780-784.

329. S. Adusumalli, J. E. Westover, D. S. Jacoby*, et al.*, *Effect of Passive Choice and Active Choice Interventions in the Electronic Health Record to Cardiologists on Statin Prescribing: A Cluster Randomized Clinical Trial.* JAMA Cardiology, 2021. **6**(1): p. 40-48.

330. Y. J. Li, W. S. Lee, Y. L. Chang*, et al.*, *Impact of a Clinical Decision Support System on Inappropriate Prescription of Glucose-lowering Agents for Patients With Renal Insufficiency in an Ambulatory Care Setting.* Clin Ther, 2022. **44**(5): p. 710-722.

331. K. M. Muylle, K. Gentens, A. G. Dupont*, et al.*, *Evaluation of an optimized context-aware clinical decision support system for drug-drug interaction screening.* Int J Med Inform, 2021. **148**: p. 104393.

332. T. M. Maddox, *Clinical Decision Support in Statin Prescription—What We Can Learn From a Negative Outcome.* JAMA Cardiology, 2021. **6**(1): p. 48-49.

333. UK Home Office. *Drug strategy 2017*. 2017 [cited 27 January 2023]; Available from: https://www.gov.uk/government/publications/drug-strategy-2017.

334. R. J. Gatchel, D. D. McGeary, C. A. McGeary*, et al.*, *Interdisciplinary chronic pain management: past, present, and future.* Am Psychol, 2014. **69**(2): p. 119-30.

335. J. Frkovich, H. Hedrick, A. R. Anakaraonye*, et al.*, *Opioid-Related Public Health Communication Campaigns: An Environmental Scan.* Am J Health Promot, 2022. **36**(6): p. 913-919.

336. J. M. Rath, E. C. Hair, A. A. Barton*, et al.*, *Early Evidence of an Opioid Education Campaign: A Case Study of Rhode Island.* J Public Health Manag Pract, 2020. **26**(3): p. 252-258.

337. L. Maher and G. Dertadian, *Qualitative research.* Addiction, 2018. **113**(1): p. 167-172.

338. A. T. Weil, *Drug, Set, and Setting: The Basis for Controlled Intoxicant Use.* Journal of Psychoactive Drugs, 1984. **16**(3): p. 271-271.

339. E. Denny and A. Weckesser, *Qualitative research: what it is and what it is not.* BJOG, 2019. **126**(3): p. 369-369.

340. J. B. Dahl, R. V. Nielsen, J. Wetterslev*, et al.*, *Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review.* Acta Anaesthesiol Scand, 2014. **58**(10): p. 1165-81.

341. K. Bykov, B. T. Bateman, J. M. Franklin*, et al.*, *Association of Gabapentinoids With the Risk of Opioid-Related Adverse Events in Surgical Patients in the United States.* JAMA Netw Open, 2020. **3**(12): p. e2031647.

342. T. Bongiovanni, S. Gan, E. Finlayson*, et al.*, *Prolonged use of newly prescribed gabapentin after surgery.* J Am Geriatr Soc, 2022. **70**(12): p. 3560-3569.

343. P. Schober and T. R. Vetter, *Logistic Regression in Medical Research.* Anesth Analg, 2021. **132**(2): p. 365-366.

344. J. C. Stoltzfus, *Logistic Regression: A Brief Primer.* Acad Emerg Med, 2011. **18**(10): p. 1099-1104.

345. W. J. Meurer and J. Tolles, *Logistic Regression Diagnostics: Understanding How Well a Model Predicts Outcomes.* JAMA, 2017. **317**(10): p. 1068-1069.

346. L. Thomas and E. M. Reyes, *Tutorial: Survival Estimation for Cox Regression Models with Time-Varying Coefficients Using SAS and R.* Journal of Statistical Software, Code Snippets, 2014. **61**(1): p. 1 - 23.

347. H. J. Whitaker, C. Paddy Farrington, B. Spiessens*, et al.*, *Tutorial in biostatistics: the self-controlled case series method.* Stat Med, 2006. **25**(10): p. 1768-1797.

Appendices

Appendix 1. Medicines for managing chronic pain included in the time-series analysis

Category	Subcategory	Drug substance
Gabapentinoids		Pregabalin
		Gabapentin
Opioids	Strong opioids	Buprenorphine
		Dextromoramide Tartrate
		Fentanyl
		Hydromorphone Hydrochloride
		Methadone Hydrochloride
		Morphine Hydrochloride
		Morphine Sulfate
		Morphine Tartrate & Cyclizine Tartrate
		Oxycodone
		Oxycodone HCl/Naloxone HCl
		Oxycodone Hydrochloride
		Pentazocine Hydrochloride
		Pentazocine Lactate
		Pethidine Hydrochloride
		Tapentadol Hydrochloride
		Tramadol Hydrochloride
	Weak opioids	Codeine Phosphate
		Dextromoramide Tartrate
		Meptazinol Hydrochloride
		Nalbuphine Hydrochloride
		Dextropropoxyphene
		Co-Codamol (Codeine Phosphate /Paracetamol)
		Co-Codaprin (Codeine Phosphate /Aspirin)
		Co-Dydramol (Dihydrocodeine/Paracetamol)
		Co-Proxamol (Dextropropoxyphene HCl/Paracetamol)
	Drugs for opioid dependence	Buprenorphine Hydrochloride
		Methadone Hydrochloride
		Buprenorphine HCl/Naloxone HCl
Antidepressants	Tricyclic Antidepressants (TCAs)	Amitriptyline Hydrochloride
		Amoxapine
		Clomipramine Hydrochloride
		Dosulepin Hydrochloride
		Doxepin

		Imipramine Hydrochloride
		Lofepramine Hydrochloride
		Maprotiline hydrochloride
		Mianserin Hydrochloride
		Nortriptyline
		Trazodone Hydrochloride
		Trimipramine Maleate
	Serotonin-Noradrenaline Re-uptake Inhibitors (SNRIs)	Duloxetine Hydrochloride
		Venlafaxine
	Selective Serotonin Re-uptake inhibitors (SSRIs)	Citalopram Hydrobromide
		Citalopram Hydrochloride
		Escitalopram
		Fluoxetine Hydrochloride
		Fluvoxamine Maleate
		Paroxetine Hydrochloride
		Sertraline Hydrochloride
	Monoamine-Oxidase Inhibitors (MAOIs)	Isocarboxazid
		Moclobemide
		Phenelzine Sulfate
		Tranylcypromine Sulfate
	Other antidepressant drugs	Agomelatine
		Flupentixol Hydrochloride
		Mirtazapine
		Nefazodone Hydrochloride
		Reboxetine
		Vortioxetine
	Long-term	Flurazepam Hydrochloride
		Nitrazepam
		Chlordiazepoxide Hydrochloride
		Diazepam
		Clobazam
	Short term	Loprazolam Mesylate
		Lormetazepam
		Temazepam
		Triazolam
		Alprazolam
		Bromazepam
		Lorazepam
		Oxazepam
		Midazolam Hydrochloride

		Midazolam Maleate
Benzodiazepines	Hypnotics	Flurazepam Hydrochloride
		Loprazolam Mesylate
		Lormetazepam
		Nitrazepam
		Temazepam
		Triazolam
	Anxiolytics	Alprazolam
		Bromazepam
		Chlordiazepoxide Hydrochloride
		Diazepam
		Lorazepam
		Oxazepam
	Epilepsy	Clobazam
		Midazolam Hydrochloride
		Midazolam Maleate

Appendix 2. Amended protocol approved by ISAC in CPRD

Applicants must complete all sections listed below Applications with sections marked 'Not applicable' without justification will be returned as invalid
1. Flow chart to identify the code list for chronic pain Study Title (Max. 255 characters, including spaces) Investigating the risk of serious adverse events associated with the use of gabapentinoids in patients with chronic non-cancer pain in primary care
2. Lay Summary (Max. 250 words) Gabapentin and pregabalin are a group of medicines known as gabapentinoids, commonly used for treating epilepsy and neuropathic pain (a complex chronic pain condition caused by damage or disease that results in problems with signals from the nerves). Over the past decade, the number of prescriptions of gabapentinoids has increased dramatically in the United Kingdom (UK), especially in patients with various chronic pain conditions, such as low back pain and arthritis. Meanwhile, the number of deaths involving gabapentinoids has increased too. Due to the increasing concerns in misuse and overuse, gabapentinoids were classified as controlled drugs from April 2019, and thereafter all prescriptions need to be hand-signed by doctors. Studies in other countries had found a higher risk of opioid-related deaths when patients combined gabapentinoids with opioids. However, the risks of other serious events potentially associated with gabapentinoids, such as bone fracture, suicide and drug-related death, are still unknown in the UK. With the increasing number of gabapentinoids prescribed every year it is important to study the safety issues related to gabapentinoids and factors that potentially cause harm to patients. This study will investigate the risks of serious adverse events associated with the prescribing of gabapentinoids in patients with chronic pain conditions and identify factors that may increase the risk. The results will help general practitioners to recognise patients at higher risk of developing the adverse outcomes and avoid potential harms when prescribing these medicines. *(235 words)*
3. Technical Summary (Max. 300 words) Gabapentin and pregabalin (known as "gabapentinoids") are medicines indicated for focal seizure and neuropathic pain. In the past decade, there has been a marked increase of gabapentinoids prescribed in the United Kingdom (UK) primary care setting predominantly for patients with chronic non-cancer pain (CNCP). There is also an increase in drug-related deaths involving gabapentinoids. Due to the concern in misuse, abuse and illegal diversion, gabapentinoids were classified as controlled C drugs in the UK from 1st April 2019. Previous literature found gabapentinoids increased the risk of death in opioid users, probably by enhancing the respiratory inhibition led by opioids. Furthermore, case reports found a risk of suicide in gabapentinoid users. However, there is currently no study assessing these safety issues using healthcare databases in the UK. This study aims to evaluate the risk of serious adverse events in gabapentinoid users with CNCP by different epidemiology study designs using a UK primary care database. Firstly, a cross-sectional study will describe the trend and pattern of gabapentinoid utilisation in patients with CNCP by using data from CPRD. Secondly, a matched-cohort study will assess the prevalence of bone fracture, drug-related death and suicide between gabapentinoids users and their matched control by using CPRD linking to HES and ONS death registry. Thirdly, a nested case-control study will investigate the effect of combining gabapentinoids with other analgesics on drug-related death. Finally, two self-controlled studies will assess the risk of bone fracture and suicide (both suicidal behaviour and completed suicide) in different periods of exposure in gabapentinoid users with CNCP. The results of the study will

provide important medication safety information to inform clinical decision-making. It will help general practitioners identify risk factors that may increase the risk of adverse events during the period that needs strict monitoring and reduce the risk of gabapentinoids. *(298 words)*

4. Outcomes to be Measured

Serious adverse events related to gabapentinoids: hospital admission due to bone fracture of major arthrosis (exclude stress and pathological bone fracture); drug-related death; hospital admission or death due to suicide.

5. Objectives, Specific Aims and Rationale

This study aims to evaluate the risk of serious adverse events in gabapentinoid users with chronic non-cancer pain (CNCP) in the UK primary care setting. The objectives include:

1. To describe the trend of gabapentinoid utilisation and the characteristics of gabapentinoid users in patients with CNCP.
2. To estimate the prevalence of serious adverse events, i.e. bone fracture, drug-related death, suicide in gabapentinoid users and non-users in a CNCP population considering their demographic and disease characteristics.
3. To investigate the association between exposure to gabapentinoids and drug-related deaths in patients with CNCP and consider the influences of different analgesics, e.g. benzodiazepines, opioids, anti-depressants, Z-drugs and antipsychotics.
4. To estimate the association between prescription gabapentinoid and the incidence of bone fractures and suicides in patients newly initiated with gabapentinoid, and consider the proximity of events in different periods close to gabapentinoid initiation.

Gabapentinoids have been increasingly used in patients with CNCP, but the utilisation pattern of gabapentinoids and its association with patients' characteristics have not been studied in the UK. Understanding the characteristics of gabapentinoid users, especially those long-term or high-dose users, helps to further identify patients who are at higher risk of developing serious adverse events. The increasing number of serious adverse events, i.e. drug-related death, suicide and bone fracture has been reported in the large population of gabapentinoid users, although the incidence rates were relatively rare. However, the causes, onset and risk factors associated with serious adverse events related to gabapentinoids have not been fully understood. To avoid potential biases, this study will take different design approaches to study the association between risk factors and the rare, severe adverse events.

6. Study Background

Gabapentin and pregabalin (also known as gabapentinoids) are medicines indicated for managing epilepsy and neuropathic pain with mild to moderate adverse events (1-5). Gabapentinoids were considered to be relatively safe according to their pharmacological characteristics and evidence from clinical trials. However, in the past decade, with the marked increase in the number of gabapentinoid items prescribed annually (6-8) and the rapid growth of gabapentinoid-related death, concerns on safety issues associated with gabapentinoids have been raised. The rapid increase of gabapentinoid utilisation was associated with the off-label use (indications other than epilepsy and neuropathic pain) which has been identified in 50% of the gabapentinoid users in the United Kingdom (UK) in 2017 (6), predominately for chronic pain, such as low back pain, arthritis, sciatica and fibromyalgia (9-12). Due to the increasing concerns in drug misuse, illegal diversion and drug abuse (13), gabapentinoids were classified as controlled drugs in the UK since April 2019 (14). Nevertheless, the epidemiological study of serious adverse events associated with gabapentinoids such as drug-related death, bone fracture and suicide events in the UK is still lacking (15).

Gabapentinoids were increasingly detected in post-mortem studies in many countries (16-19). In the United Kingdom (UK), data published by Office for National Statistics (ONS) indicated that the number of deaths involving gabapentin and pregabalin in England and Wales has increased from 12 in 2012 to 272 in 2018 (20, 21). Of the deaths involving gabapentinoids reported by Coroners in London and South East London from January 2016 to December 2017, non-heroin opioids were the most frequent concomitant drugs (19). Meanwhile, nested case-control studies conducted in Canada found that gabapentin and pregabalin were associated with the increased risk of opioid-related death (22, 23). However, those studies focused on opioid users and evaluated gabapentinoids' effect on opioid-related mortality, and hence disregarded the gabapentinoid-related mortality which may attribute from intentionally and unintentionally drug overdose or abuse due to the euphoric effects (24). Therefore, the association between gabapentinoids and drug-related deaths caused by drug overdose and poisoning remained unknown.

Several previous studies reported cases of suicidal ideation or suicidal behaviour related to gabapentinoids, but the occurrence time of this behaviour is still inclusive. In the UK, Andersohn *et al.* (2010) identified three cases of suicidal ideation or behaviour including gabapentin and no case for pregabalin from 44,300 patients with epilepsy registered in CPRD during 1990-2005 (25). In the United States (US), a cohort study identified 228 attempted suicide and 8 completed suicide in gabapentin users; 9 attempted suicide and no completed suicide for pregabalin users between July 2001 and December 2006 from the HealthCare Integrated Research Database (26). In Sweden, a recent self-controlled case series study identified 10,026 (5.2%) gabapentinoid users who were treated for suicidal behaviour or died from suicide from a national database from 2006 to 2013 (27). In this study, gabapentinoid exposure was found to be associated with an increased risk of suicide behaviour and death from suicides. The exposure to gabapentinoids was defined as two consecutive prescriptions on gabapentinoids apart less than three months, which means that new users or short-term users were not considered in the analysis. In contrast, case reports suggested a rapid occurrence of suicide ideation or behaviour after administration of gabapentinoids (32, 33), so suicidal behaviours seem more likely to happen after the first prescription of gabapentinoids and discontinued.

The sedative effects, such as dizziness and sleepy are the common adverse effects of pregabalin (13-29%) and gabapentin (19%) (1, 4). Previous nested case-control studies conducted in Canada and Taiwan found that gabapentinoid-related dizziness was associated with a higher risk of fall in elder patients (28, 29). Another cross-sectional study used data from US FDA Adverse Event Reporting System and the Japanese Adverse Drug Event Report database found that the fall-related adverse events (i.e. somnolence, dizziness, loss of consciousness) often happened within one week after the administration of the subject's first prescription (with a median of 2 days) (30).

Therefore this study will focus on the large population of patients with CNCP (including neuropathic pain) who were assumed to be under a high risk of exposure to and harms of gabapentinoids. The risk of serious adverse events will be analysed in different types of study design to better fit to the characteristic of each outcome.

7. Study Type

This project will primarily be a hypothesis-generating study. An initial descriptive study will provide insight into the characteristics of gabapentinoid users in patients with CNCP and their drug utilisation pattern. After that, the prevalence of serious adverse events (i.e. bone fracture, drug-related death and suicide) will be explored by comparing gabapentinoid users and their matched cohort in patients with CNCP; further hypothesis testing studies will be carried out after the risk of serious adverse events were detected. Namely, the impact of any exposure to gabapentinoids, dose-related gabapentinoids

exposure, duration of gabapentinoids exposure and combined exposure with other drugs on the incidence of serious adverse events.

8. Study Design

This project contains several study designs to investigate the study outcomes, including a cross-sectional study, followed by a matched cohort study, a nested case-control study, and self-controlled case-crossover and case-series studies using CPRD GOLD and Aurum and the linkage to Hospital Episode Statistics (HES) data and ONS Mortality Data. CPRD GOLD and Aurum will provide details of patients' characteristics, disease history and drug utilisation. Data linked to HES will provide hospital admission due to severe adverse events (e.g. bone fracture and suicidal behaviour) associated with gabapentinoids. Drug-related death and completed suicide associated with gabapentinoids will be obtained by linking CPRD primary care data to ONS Mortality Data.

9. Feasibility counts

Around 400,000 new gabapentinoids users were identified from CPRD GOLD in the period of 2007-2017 (6). It is anticipated that around 200,000 gabapentinoid users with CNCP will be identified from CPRD GOLD and the number of the cohort may double in CPRD Aurum because Aurum has more than twice the population of GOLD. The prevalence of CNCP in the UK was found to range from 35.0% to 51.3% (31) so that at least 15.8 million patients with CNCP would be identified. Based on the estimation of gabapentinoid users, it is anticipated that around 200,000 gabapentinoid users with CNCP will be identified from CPRD. Among them, 2,000 cases of bone fracture, 300 cases of suicidal outcome and 15 cases of drug-related death would be identified in gabapentinoid users with CNCP according to the prevalence reported in the previous literature (32-34). In the CNCP population, around 1044 cases of drug-related death would be identified.

10. Sample size considerations

The proposed matched-cohort study aims to explore the prevalence of rare adverse events in gabapentinoids users and compare to non-users. Differences may be observed between groups but very possible to be statistically insignificant because matched-cohort study was not designed to identify rare outcomes. here a sample size calculation was applied to the more common adverse events of bone fracture in the matched-cohort study to explore if any statistical difference can be identified. Of the three serious adverse events in this study, the incidence of bone fracture is higher than the other two rare adverse events (drug-related death and suicide). According to the incidence rate of bone fracture identified from previous literature (33), the sample size required for studying bone fracture was calculated by using the method of Kelsey in Openepi (35) with the statistical power of 80% and a two-sided type-1 error of 5% as the significant level. As a previous study found a 1.79 odds ratio of bone fracture in gabapentinoids compared to controls (28), by ranging the effect sizes (relative risk) from 1.1 to 2.0, the required sample size for statistical analyse is listed in the following table. A significant difference in bone fractures between gabapentinoids user and non-user should be expected in the matched-cohort study.

	Incidence rate in unexposed	RR=1.1	RR=1.2	RR=1.3	RR=1.4	RR=1.5	RR=2.0
Bone fracture							
Exposure	3.6% (Curtis et al. 2016)	27757	7095	3223	1852	1211	335
Control (1:5 matched)		138783	35471	16111	9259	6052	1673

The statistical power can increase when cases were matched to more controls in nested case-control studies (36). Here we used 1:10 matching as an example for the nested case-control study to identify the risk of drug-related death in patients with CNCP. The proportion of exposure to gabapentinoids in control group was anticipated to be around

4% based on previous studies (22, 23). The sample size was calculated with the statistical power of 80% and a two-sided type-1 error of 5% as the significant level (37). When matching cases of drug-related deaths 1:10 to controls in the case-control study, 1071 cases and 10710 controls were required to support a statistically significant difference. Sample size calculation is not needed in the self-controlled case cross-over or case-series study.

11. Planned use of linked data (if applicable):

This study will use the primary care data in CPRD Gold (from January 1987 to December 2019) and CPRD Aurum (from January 1995 to December 2019) in linkage with HES-APC, HES-A&E, ONS Death Registry and IMD small area level data (listed as the following table). Clinical, therapy and consultation data in CPRD primary care data will be used.

Database	Time period or dataset	Outcome
HES APC	April 1997- December 2018	Bone fracture, suicida
HES A&E	April 2007- December 2018	Bone fracture, suicida
ONS Death Registry	2nd January 1998 - 14th January 2019	Drug-related death, c
Small area level data	2015 English Index of Multiple Deprivation	Patient-level IMD and
	England and Wales Rural Urban Classification	Patient-level urban ar

The study period of each study design will start from the earliest available linked data to the latest available date overlapped in the linked databases (currently November 2018 in HES):

- January 1998 to December 2019 for the matched cohort study
- January 1998 to January 2019 for drug-related death in the nested case-control study
- April 2007 to December 2019 for fracture and completed suicide in the self-controlled case-crossover study, January 1998 to January 2019 for suicidal behaviour in self-controlled case-series study

12. Definition of the Study population

Patients with CNCP will be the population of interest in this study. They will be identified from CPRD primary care databases from 1993 to 2019 and followed up from the date of the first CNCP record until the end of registration (i.e. leave the practice, died, diagnosed with cancer or to the latest available time whichever comes earlier in the database). The target study population is adult gabapentinoid users with CNCP, i.e. those who were issued with at least one gabapentinoid prescription and had a diagnosis of CNCP (identified by Read codes in Appendix 1) in the CPRD Gold and Aurum from 1 Jan 1993 to 31 December 2019. Patients will be excluded from this study if they meet the following criteria: (1) aged less than 18 years on the date of CNCP diagnosis; (2) had a diagnosis of cancer before the CNCP diagnosis date; or (3) had at less than 6 months of up-to-standard CPRD records before the CNCP diagnosis date. In addition, a matched control to the gabapentinoid users will also be identified (Section 11). The study cohort who are eligible for the linkage of CPRD with HES APC/A&E and ONS Death Registry will be selected to assess the incidence of serious adverse events.

13. Selection of comparison group(s) or controls

The comparison groups will be included in the matched cohort study and nested case-control study designs; no comparison group is needed in the self-control study.

To estimate the incidence of serious adverse events in the matched cohort study, each study cohort (adult gabapentinoid user with CNCP) will be matched to up to 5 controls from the cohort of patients with CNCP by propensity score for confounders related to the treatment of gabapentinoids.

In the nested case-control study, each case of drug-related death will be matched to 10 controls who do not have a record of drug-related death on the event date by incidence density sampling in the study cohort (adult gabapentinoid user with CNCP). Cases will be matched to the controls by disease risk score to balance the confounding factors and increase statistical efficiency.

Variables of confounders associated with prescribing of gabapentinoids before the first index date of gabapentinoids will be considered for calculating the propensity score, including year of cohort entry date, duration of follow up, demographic characteristics (e.g. age at the date prescribed first gabapentinoids, gender), practice region, comorbidity (e.g. substance misuse or abuse, mental health disease such as depression and anxiety, osteoporosis, Charlson comorbidity index score, etc), lifestyle (e.g. smoking status at the index date of gabapentinoids and defined as non-smoker or smoker, BMI at the index date of gabapentinoids, alcohol use disorder, other lifestyle factors that may potentially relate to CNCP, socio-economic status, etc), medication history (Appendix 4).

14. Exposures, Outcomes and Covariates

Exposure

'Exposure to gabapentinoids' will be identified by prescriptions on gabapentinoids in CPRD primary care database. The length of each episode will be estimated according to the amount prescribed and the available dose instruction in therapy recording or in drug indications. 'Interruption' of exposure is defined as a gap longer than 14 days between two prescriptions, which means two continuous prescriptions with a gap less or equal to 14 days will be defined as one episode. 'Concurrent exposure' is defined as any prescription of opioid, benzodiazepines, anti-depressants z-drugs and antipsychotics in a fixed time period (e.g. 30 days) before or after the exposure to gabapentinoids. For the exposure to gabapentinoids and concurrent medications, dose, duration and prescriptions will be calculated. Patients will be further categorised by medication utilisation.

Outcomes

Incidents users of gabapentinoids are defined as patients with the first-ever prescription of gabapentinoids in the year. Patients with any prescription on gabapentinoids after the year of the first prescription will be defined as prevalent users. The annual proportion of incident or prevalent user will be derived from dividing the number of incidence or prevalent user by the number of gabapentinoid users in the year of study. The demographic characteristics, disease history and medication utilisation history of gabapentinoids users will be described as proportion in each year.

Serious adverse events in this study are hospital admissions due to bone fracture, drug-related death and suicide (suicidal behaviour and completed suicide) which will be identified by the ICD-10 codes (Appendix 2). 'Bone fracture' event will be identified by ICD-10 codes from CPRD-HES linked data. 'Drug-related death' is defined as deaths related to drug poisoning and will be identified by ICD-10 codes from CPRD-ONS linked data. 'Suicide' event is a composite outcome including suicidal behaviour and completed suicide. In this study, suicidal behaviour is defined as 'any act of self-poisoning or self-injury, irrespective of the apparent purpose' according to the definition given by the National Institute for Health and Clinical Excellence (NICE) guidelines for self-harm (38). Suicidal behaviour includes all self-harm behaviour regardless of the purpose will be identified by ICD-10 codes from HES data. Completed suicide is defined as death because of suicide and will be identified by ICD-10 codes from ONS Death Registry Data.

Time to event (TTE) is defined as the time between index date and the date cases happen. The TTE for bone fracture, drug-related death and suicide will be described in the gabapentinoid user cohort.

Covariates

Comorbidity (e.g. substance misuse or abuse, mental health disease such as depression, anxiety, osteoporosis, chronic disease, Charlson comorbidity index score, etc) and individual lifestyle characteristics (e.g. smoking status at the index date of gabapentinoids and defined as non-smoker or smoker, BMI at the index date of gabapentinoids, alcohol use disorder, other lifestyle factors that may potentially relate to CNCP, socio-economic status, etc) after the index date of gabapentinoids will be identified by Read codes from CPRD primary care database and used as covariates to adjust for outcomes. In addition, opioids and sedatives (benzodiazepines, antidepressants, z-drugs, antipsychotics) prescriptions will be extracted by DM+D code from CPRD Aurum and Gemscript code from CPRD GOLD to adjust for outcomes.

15. Data/ Statistical Analysis

Descriptive statistics will be used to report patients' characteristics including age, gender, duration of CNCP and history of comorbidity in the study cohort. For the exposure to gabapentinoids and concurrent medications, the dose and duration will also be described.

Cox proportional hazard models will be adapted for patient-time outcomes (i.e. hospital admission due to bone fracture, drug-related death, the composite outcome on suicide in the matched cohort study) to compare the risk ratio (HR) estimates with 95% confidence interval (95% CI) between exposure and control groups. The outcomes will be adjusted for covariates mentioned before (section N).

Conditional logistic analysis will be conducted on binary outcomes to explore the odds ratio (OR) of the outcomes in gabapentinoids exposure group and control group with 95% CI. The association will be adjusted by covariates. Poisson regression will be adapted in case-series study (i.e. outcome on bone fracture and suicidal behaviour) to generate the incidence rate ratio and corresponding 95% CI after adjusting for the covariates.

Sensitivity analysis will be conducted by narrowing or expanding the inclusion criteria of exposure and covariates. For instance, the definition of incident user may be expanded to users who were not prescribed gabapentinoids in the previous 12 months in the matched-cohort study; the fixed time period to measure concurrent exposure and the number of days follow-back will be extended in the nested case-control study; the length of study period may be changed in self-controlled study. Subgroup analysis will separate gabapentin and pregabalin and stratify patients by their characteristics.

16. Plan for addressing confounding

Confounding of age, gender and GP practices will be addressed in the cohort matching process. Other factors (e.g. medication, comorbidities, lifestyle factors) that were previously reported to be associated with the study outcomes will be adjusted as covariates in the statistical analysis.

17. Plans for addressing missing data

Missing data on exposure and outcomes will not be identified because they mean an absence of condition and should be labelled as no exposure or no outcome. The missing data of concern in this study will mainly be in the variables related to prescription such as quantity, daily dose and duration of prescriptions. Since the missing was assumed to be random, multiple imputation will be applied to create estimated data to replace the missing data (39). For the covariates at cohort entry (i.e. disease history and lifestyle), complete-case analysis will be used when the number of missing was small. If there is a large number of values missing, multiple imputation would be used to replace the missing data.

18. Patient or user group involvement

Specialists from the perspective of prescriber and policymakers have been consulted to understand the situation of prescribing gabapentinoids and feedback from patients. The consultation interviews involved (1) GPs to explore their experiences about prescribing

gabapentinoids, (2) GP pharmacists to understand perceptions on issues related prescribing gabapentinoids and (3) a control drug accountable officer from NHS to know the concerns on gabapentinoids, current regulations and the areas that are lacking of research evidence to inform regulations. Gabapentinoids users and patients with CNCP were planned to be involved for consultations during the process of the study.

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

Results of this study will be disseminated as papers in peer-reviewed scientific journals and as poster or oral presentations in academic conferences after project completion.

Conflict of interest statement: The investigators declare no conflict of interest.

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

Although CPRD is a primary care database covering a representative and large sample of patients in the UK, it can possibly have selection bias in processing the data collection in selected GP practices.

The recording system used in CPRD may also introduce limitations. The population of CNCP will be extracted by Read code, SNOWMED codes and Emis specific codes from CPRD primary care database and this process may lose some patients who should be eligible but do not have proper Read code or were misclassified in Read code. The misclassification can have complex reasons such as incorrect coding and invalid algorithm. There can also be unmeasured confounding factors such as personal lifestyle, workload, genetic factors. Another limitation is the prescription on gabapentinoids were assumed to be taken by the patients, which may possibly lead to bias. Furthermore, the matched cohort study will assess the risk of serious adverse outcomes after adjusting for the utilisation of other analgesics, but over the counter painkillers such as paracetamol and NSAIDs cannot be thoroughly monitored by using primary care database.

As for the study cohort, some cancer conditions (e.g. breast cancer, chronic myeloid leukaemia) are likely to have a long survival time after recovery and excluding them may lead to underrepresent of cancer patients with CNCP. However, considering the comparatively small population of long-surviving patients with cancer, this bias may not bring a huge problem to the results.

21. References

1. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2019(1).
2. Panebianco M, Al-Bachari S, Weston J, Hutton JL, Marson AG. Gabapentin add-on treatment for drug-resistant focal epilepsy. Cochrane Database of Systematic Reviews. 2018(10).
3. Panebianco M, Bresnahan R, Hemming K, Marson AG. Pregabalin add-on for drug-resistant focal epilepsy. Cochrane Database of Systematic Reviews. 2019(7).
4. Wiffen PJ, Derry S, Bell RF, Rice ASC, Tölle TR, Phillips T, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2017(6).
5. Joint Formulary Committee. British national formulary (BNF)2018.
6. Montastruc F, Loo SY, Renoux C. Trends in first gabapentin and pregabalin prescriptions in primary care in the united kingdom, 1993-2017. Jama. 2018;320(20):2149-51.
7. Johansen ME. Gabapentinoid use in the united states 2002 through 2015. JAMA Internal Medicine. 2018;178(2):292-4.
8. Appleyard T, Ashworth J, Bedson J, Yu D, Peat G. Trends in gabapentinoid prescribing in patients with osteoarthritis: a United Kingdom national cohort study in primary care. Osteoarthritis and cartilage. 2019.
9. Shanthanna H, Gilron I, Rajarathinam M, AlAmri R, Kamath S, Thabane L, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2017;14(8):e1002369.

10. Mathieson S, Maher CG, McLachlan AJ, Latimer J, Koes BW, Hancock MJ, et al. Trial of Pregabalin for Acute and Chronic Sciatica. New England Journal of Medicine. 2017;376(12):1111-20.
11. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. Cochrane Database of Systematic Reviews. 2017(1).
12. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane Database of Systematic Reviews. 2016(9).
13. Iacobucci G. UK government to reclassify pregabalin and gabapentin after rise in deaths. BMJ (Clinical research ed). 2017;358:j4441.
14. Home Office and Victoria Atkins MP. Pregabalin and gabapentin to be controlled as class C drugs 2018 [cited 2019 05 December]. Available from: https://www.gov.uk/government/news/pregabalin-and-gabapentin-to-be-controlled-as-class-c-drugs.
15. England PH. Prescribed medicines review: report. In: England PH, editor. 2019.
16. Lottner-Nau S, Övgüer B, Paul LD, Graw M, Sachs H, Roider GJTK. Abuse of pregabalin–results of the postmortem toxicology from 2010 to 2012. 2013;80(special issue):339-42.
17. Hakkinen M, Vuori E, Kalso E, Gergov M, Ojanpera I. Profiles of pregabalin and gabapentin abuse by postmortem toxicology. Forensic science international. 2014;241:1-6.
18. Eastwood JA, Davison E. Pregabalin concentrations in post-mortem blood-A two year study. Forensic science international. 2016;266:197-201.
19. Nahar LK, Murphy KG, Paterson S. Misuse and Mortality Related to Gabapentin and Pregabalin are Being Under-Estimated: A Two-Year Post-Mortem Population Study. Journal of analytical toxicology. 2019.
20. Office for National Statistics Number of drug-related deaths involving Gabapentin or Pregabalin with or without an opioid drug, England and Wales, 2018: Office for National Statistics 2018 [cited 2019 08 December]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/10713numberofdrugrelateddeathsinvolvinggabapentinorpregabalinwithorwithoutanopioiddrugenglandandwales2018.
21. Office for National Statistics. Deaths related to drug poisoning in England and Wales: 2016 registrations 2016 [cited 2019 08 December]. Available from: 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.
22. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. PLOS Medicine. 2017;14(10):e1002396.
23. Gomes T, Greaves S, van den Brink W, Antoniou T, Mamdani MM, Paterson JM, et al. Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study. Ann Intern Med. 2018;169(10):732-4.
24. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs. 2017;77(4):403-26.
25. Andersohn F, Schade R, Willich SN, Garbe E. Use of antiepileptic drugs in epilepsy and the risk of self-harm or suicidal behavior. Neurology. 2010;75(4):335-40.
26. Patorno E, Bohn RL, Wahl PM, et al. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. Jama. 2010;303(14):1401-9.
27. Molero Y, Larsson H, D'Onofrio BM, Sharp DJ, Fazel S. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden. 2019;365:l2147.
28. Cheng HH, Huang WC, Jeng SY. Anti-epileptic drugs associated with fractures in the elderly: a preliminary population-based study. Curr Med Res Opin. 2019;35(5):903-7.
29. Jetté N, Lix LM, Metge CJ, Prior HJ, McChesney J, Leslie WD. Association of antiepileptic drugs with nontraumatic fractures: A population-based analysis. Archives of Neurology. 2011;68(1):107-12.
30. Mukai R, Hasegawa S, Umetsu R, Nakao S, Shimada K, Uranishi H, et al. Evaluation of pregabalin-induced adverse events related to falls using the FDA adverse event reporting system and Japanese Adverse Drug Event Report databases. Journal of clinical pharmacy and therapeutics. 2019;44(2):285-91.

31. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ open. 2016;6(6):e010364.
32. Office for National Statistics. Deaths related to drug poisoning in England and Wales: 2018 registrations 2018 [cited 2019 08 December]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2018registrations.
33. Curtis EM, van der Velde R, Moon RJ, van den Bergh JPW, Geusens P, de Vries F, et al. Epidemiology of fractures in the United Kingdom 1988-2012: Variation with age, sex, geography, ethnicity and socioeconomic status. Bone. 2016;87:19-26.
34. Carr MJ, Ashcroft DM, Kontopantelis E, Awenat Y, Cooper J, Chew-Graham C, et al. The epidemiology of self-harm in a UK-wide primary care patient cohort, 2001-2013. BMC Psychiatry. 2016;16:53-.
35. Sullivan KM, Dean A, Soe MMJPhr. On academics: OpenEpi: a web-based epidemiologic and statistical calculator for public health. 2009;124(3):471-4.
36. Pang D. A relative power table for nested matched case-control studies. Occup Environ Med. 1999;56(1):67-9.
37. Lwanga SK, Lemeshow S, Organization WH. Sample size determination in health studies: a practical manual. 1991.
38. National Institute for Clinical Excellence. Self-harm in over 8s: short-term management and prevention of recurrence. London: NICE; 2004.
39. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. 2009;338:b2393.
40. Watson J, Nicholson BD, Hamilton W, Price S. Identifying clinical features in primary care electronic health record studies: methods for codelist development. BMJ open. 2017;7(11):e019637.
41. Office for National Statistics. Deaths related to drug poisoning in England and Wales QMI 2018 [cited 2019 18 December]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/deathsrelatedtodrugpoisoninginenglandandwalesqmi.
42. Thomas KH, Davies N, Metcalfe C, Windmeijer F, Martin RM, Gunnell D. Validation of suicide and self-harm records in the Clinical Practice Research Datalink. 2013;76(1):145-57.

22. List of Appendices

Appendix 1. Codes for chronic non-cancer pain

The codes for CNCP were integrated from the code list for back pain available on Clinical Codes website (https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/6/codelist/back-pain/) and the codes list generated based on a validated algorithm (40).

Appendix 2. Codes for exposures

The product codes for gabapentin and pregabalin were searched using CPRD Code Browser.

Appendix 3. Codes for outcomes

The code list for fracture was extracted from a published study with ICD-10 codes available on Clinical Codes website (https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/84/). The codes list for drug-related death was extracted from the ICD-10 codes used by ONS to define deaths related to drug poisoning (41). The code list for suicide was extracted from a previously published study using CPRD (42).

Appendix 4. Medications for adjusting

1. Opioids

- Buprenorphine, codeine, dextromoramide, dihydrocodeine, dipipanone, fentanyl, hydromorphone, meptazinol, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, tapentadol, tramadol (including paracetamol)
- Codeine with paracetamol (co-codamol), dihydrocodeine with paracetamol (co-dydramol)

2. Benzodiazepines
   - Flurazepam, loprazolam, lormetazepam, nitrazepam, temazapam
   - Alprazolam, chlordiazepoxide, hydrochloride, diazepam, lorazepam, oxazepam, clobazam
3. Antidepressants
   - Tricyclics: amitriptyline (including perphenazine), amoxapine, clomipramine, dosulepin, doxepin, imipramine, lofepramine, maprotiline, mianserin, nortriptyline, trazodone, trimipramine,
   - MAOIs: isocarboxazid, moclobemide, phenelzine, tranylcypromine
   - SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
   - Others: agomelatine, duloxetine, flupentixol, mirtazapine, nefazodone, oxitriptan, tryptophan, venlafaxine, vortioxetine
4. Z-drugs
   - Zaleplon, zopiclone, zolpidem
5. Antipsychotic
   - Amisulpride, aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone
   - Chlorpromazine, flupentixol, haloperidol, levomepromazine, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, sulpiride, trifluperazine, zuclopenthixol

Amendment – 28/05/2020

Selection of comparison group(s) or controls

The comparison groups will be included in the matched cohort study and nested case-control study designs; no comparison group is needed in the self-control study.

To estimate the incidence of serious adverse events in the matched cohort study, each study cohort (adult gabapentinoid user with CNCP) will be matched to up to 5 controls from the cohort of patients with CNCP by age, gender and practice.

In the nested case-control study, each case of drug-related death will be matched to 10 controls who do not have a record of drug-related death on the event date by incidence density sampling in the study cohort (adult gabapentinoid user with CNCP). Cases will be matched to the controls by disease risk score to balance the confounding factors and increase statistical efficiency.

(Deleted information on propensitiy score matching)

Appendix 3. The keywords for searching chronic pain code lists

Category	Keywords
Symptoms	Pain Aching Ache
Neuropathic pain	Neuropathy Neuralgia Neuropathic Neuritis Sciatic
Headache	Migraine Headache Hemicranias
Fibromyalgia	Fibromyalgia Myalgia
Arthritis	Arthritis Arthritic Arthralgia Arthropath* Rheumatica Rheumatism
Back pain	Lumbago Lumbalgia Musculoskeletal Spondylitis Ankylosis Neck & injur* Stiff & neck Back & stiff Spinal fracture Spinal meningocele Spinal meningeal Spinal cord lesion Spinal Stenosis Spinal cord anomalies Spin* & injur* Fracture & neck Fracture & spine Neck sprain Neck disorder Neck symptom Neck joint abnormal Sacroiliac Strain Joint Syndrome Joint disorder Joint symp Instability Coccygodynia Spasm of back muscles Facet joint syndrome Lipoma of spinal Fracture & osteoporosis Hypermobility of the coccyx Sprain

*Note: * Open ending search*

Appendix 4. ICD-10 codes for fracture

ICD-10 code	Description
T02	Fractures involving multiple body regions
T02.0	Fractures involving head with neck
T02.1	Fractures involving thorax with lower back and pelvis
T02.2	Fractures involving multiple regions of one upper limb
T02.3	Fractures involving multiple regions of one lower limb
T02.4	Fractures involving multiple regions of both upper limbs
T02.5	Fractures involving multiple regions of both lower limbs
T02.6	Fractures involving multiple regions of upper limb(s) with lower limb(s)
T02.7	Fractures involving thorax with lower back and pelvis with limb(s)
T02.8	Fractures involving other combinations of body regions
T02.9	Multiple fractures, unspecified
T08	Fracture of spine, level unspecified
T10	Fracture of upper limb, level unspecified
T12	Fracture of lower limb, level unspecified
T14.2	Fracture of unspecified body region
S02	Fracture of skull and facial bones
S02.0	Fracture of vault of skull
S02.1	Fracture of base of skull
S02.2	Fracture of nasal bones
S02.3	Fracture of orbital floor
S02.4	Fracture of malar and maxillary bones
S02.5	Fracture of tooth
S02.6	Fracture of mandible
S02.7	Multiple fractures involving skull and facial bones
S02.8	Fractures of other skull and facial bones
S02.9	Fracture of skull and facial bones, part unspecified
S12	Fracture of neck
S12.0	Fracture of first cervical vertebra
S12.1	Fracture of second cervical vertebra
S12.2	Fracture of other specified cervical vertebra
S12.7	Multiple fractures of cervical spine
S12.8	Fracture of other parts of neck
S12.9	Fracture of neck, part unspecified
S22	Fracture of rib(s), sternum and thoracic spine
S22.0	Fracture of thoracic vertebra
S22.1	Multiple fractures of thoracic spine
S22.2	Fracture of sternum
S22.3	Fracture of rib
S22.4	Multiple fractures of ribs
S22.5	Flail chest
S22.8	Fracture of other parts of bony thorax
S22.9	Fracture of bony thorax, part unspecified
S32	Fracture of lumbar spine and pelvis
S32.0	Fracture of lumbar vertebra

S32.1	Fracture of sacrum
S32.2	Fracture of coccyx
S32.3	Fracture of ilium
S32.4	Fracture of acetabulum
S32.5	Fracture of pubis
S32.7	Multiple fractures of lumbar spine and pelvis
S32.8	Fracture of other and unspecified parts of lumbar spine and pelvis
S42	Fracture of shoulder and upper arm
S42.0	Fracture of clavicle
S42.1	Fracture of scapula
S42.2	Fracture of upper end of humerus
S42.3	Fracture of shaft of humerus
S42.4	Fracture of lower end of humerus
S42.7	Multiple fractures of clavicle, scapula and humerus
S42.8	Fracture of other parts of shoulder and upper arm
S42.9	Fracture of shoulder girdle, part unspecified
S52	Fracture of forearm
S52.0	Fracture of upper end of ulna
S52.1	Fracture of upper end of radius
S52.2	Fracture of shaft of ulna
S52.3	Fracture of shaft of radius
S52.4	Fracture of shafts of both ulna and radius
S52.5	Fracture of lower end of radius
S52.6	Fracture of lower end of both ulna and radius
S52.7	Multiple fractures of forearm
S52.8	Fracture of other parts of forearm
S52.9	Fracture of forearm, part unspecified
S62	Fracture of wrist and hand level
S62.0	Fracture of navicular [scaphoid] bone of hand
S62.1	Fracture of other carpal bone(s)
S62.2	Fracture of first metacarpal bone
S62.3	Fracture of other metacarpal bone
S62.4	Multiple fractures of metacarpal bones
S62.5	Fracture of thumb
S62.6	Fracture of other finger
S62.7	Multiple fractures of fingers
S62.8	Fracture of other and unspecified parts of wrist and hand
S72	Fracture of femur
S72.0	Fracture of neck of femur
S72.1	Pertrochanteric fracture
S72.2	Subtrochanteric fracture
S72.3	Fracture of shaft of femur
S72.4	Fracture of lower end of femur
S72.7	Multiple fractures of femur
S72.8	Fractures of other parts of femur
S72.9	Fracture of femur, part unspecified

S82	Fracture of lower leg, including ankle
S82.0	Fracture of patella
S82.1	Fracture of upper end of tibia
S82.2	Fracture of shaft of tibia
S82.3	Fracture of lower end of tibia
S82.4	Fracture of fibula alone
S82.5	Fracture of medial malleolus
S82.6	Fracture of lateral malleolus
S82.7	Multiple fractures of lower leg
S82.8	Fractures of other parts of lower leg
S82.9	Fracture of lower leg, part unspecified
S92	Fracture of foot, except ankle
S92.0	Fracture of calcaneus
S92.1	Fracture of talus
S92.2	Fracture of other tarsal bone(s)
S92.3	Fracture of metatarsal bone
S92.4	Fracture of great toe
S92.5	Fracture of other toe
S92.7	Multiple fractures of foot
S92.9	Fracture of foot, unspecified

Appendix 5. Statistical models

Logistic regression

Logistic regression is an extension to linear regression that could fit continuous or binary independent variables (i.e. X variables) and binary dependent variables (i.e. Y variable) in one regression model [343]. Logistic regression applied a logit function to transform the log odds to probability which is then able to fit into a linear regression:

$$\ln\left(\frac{\hat{Y}}{1-\hat{Y}}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots \beta_i X_i$$

where the left of the equation is the logit of the probability and the right side of the equation is a simple linear regression [344]. Unlike linear regression, the fitting process applied in logistic model fitting is the maximum likelihood estimation [344]. The exponentiated logistic regression slope coefficient (e^{β}) in logistic regression can be interpreted as an odds ratio indicating the change in odds of the outcome when the independent variable changes [343].

Assumptions for a logistic regression include the independence of errors, linear relationship between covariates and the logit-transformed outcome, no multicollinearity among covariates and no strong influential outliers [344]. The accuracy of a logistic regression model can be judged in two aspects: (1) discrimination, the ability to assign the right risk of the outcome to the patients, which was tested by the area under the receiver operating characteristic curve; (2) calibration, the ability to assign the correct average absolute level of risk, tested by Hosmer-Lemeshow test [345].

Survival analysis

Survival analysis is a common way to study the time between study entry and a subsequent outcome concerning censoring, originally designed to study the time from treatment until death [247]. Survival analysis accounts for the censoring in the follow-up period [245]. Typical statistical models for survival analysis includes nonparametric methods such as the Kaplan-Meier estimator and log-rank test, semiparametric methods such as Cox proportional hazard model, and parametric methods such as the parametric proportional hazards model and accelerated failure time model [245, 249].

Survival analysis consists of two functions: the survival function and the hazard function. The survival function S(t) is the probability that a patient survives from the start of follow-up to a specific time t in the future [246]. The Kaplan-Meier method plots S(t) against t to estimate the survival curve from the start of follow-up. Log-rank test is a common way to compare two survival curves (i.e. Kaplan-Meier estimate survival curve), whose null hypothesis is there is no difference between the tested survival curves [247]. A log-rank test can be seen as a univariate test of the association between the group divider (for example, gabapentinoid exposure is the group divider in this project because the two survival curves for comparison are for gabapentinoid users and non-users) and the survival time of the outcome. The Kaplan-Meier estimate and the log-rank test share the same assumptions: (1) censoring is not related to the survival prospects; (2) the survival probabilities are the same over time and same for patients enrolled early and late; (3) the event date can be clearly defined [248].

When the estimation of survival needs to account for more than one influential factor, the log-rank test does not work. In this study, the Cox proportional hazard model was adapted to study the association between gabapentinoid exposure and the risk of serious adverse events.

The Cox proportional hazard model adopted an Aalen-Breslow estimator of the cumulative hazard function and can be described as follow:

$$h(t|x) = h_0(t)e^{\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p}$$

where h(t|x) is the expected hazard at time t for a subject with a set of predictors x_1, …, x_p, $h_0(t)$ is the baseline hazard function when all predictors are equal to 0, and β_1, …, β_p are the model parameters describing the effect of the predictors on the overall hazard [249]. The Cox model provides *hazard ratios (HR)*, which is the ratio of the predicted hazard function h(t|x) under two different values of a predictor variable x_p.

A cause-specific proportional hazard model is an extension of the Cox proportional hazard model that censors the competing events rather than leaving them in the observation cohort [250]. Since patients were removed from the observation cohort at the point of competing risk occurrence, the hazard ratio of the cause-specific proportional hazard model is interpreted as “among those patients who did not experience the event of interest or a competing event”.

A Cox proportional hazard model with time-varying covariates is another extension of the Cox proportional hazard model [266]. Time-varying covariates are defined as covariates that change over time during the follow-up period [266]. The hazard of failure in a Cox proportional hazard model with time-varying covariates can be described as follow:

$$h(t|x) = h_0(t)\exp\{g(\beta, t)X\}$$

where β is a vector of coefficients and g(β,t) is the function of time as specified in the analysis [346]. The g(β,t) function is generally a simple function such as g(β,t)= βG(t), where G(t) ={g1(t), g2(t), ….}.

The primary assumption of the Cox proportional hazard model is that the hazard ratio is assumed to remain constant throughout the follow-up between the values of the predictors, regardless of the change in underlying hazard over time [249], which also applies to the cause-specific proportional hazard model. This assumption could be tested by plotting Schoenfeld residuals over time after the regression and comparing the log-log transformation of the Kaplan-Meier survival curves. The Schoenfeld residuals should be a random scatter centred on zero to fulfil the assumption. The log-log transformation of the Kaplan-Meier curve for the different categories should be parallel and not intersect [249]. Other assumptions include the covariates being time-independent, which means the variables in individual patients do not change over time [245] and the general assumption of survival analysis of uninformative censoring [245].

Self-controlled case series analysis

In the SCCS study, events are assumed to arise in individuals as a non-homogeneous, age-dependent Poisson process, where only individuals that experienced the event are sampled [347]. Let n_i denote the number of events observed for individual *i* ($n_i \geq 1$). The observation period is split into intervals by age groups, indexed by *j*, and risk periods, indexed by *k*. Reference groups of *i* and *j* are denoted as 0. Let e_{ijk} denote the time of individual *i* remain in age group *j* and risk period *k*. The incidence function is assumed [347]:

$$\lambda_{ijk} = \exp(\phi_i + \alpha_j + \beta_k)$$

where ϕ_i represents the individual *i*'s baseline incidence rate, α_j represents an age group and β_k represents the effect for risk group k, where $\alpha_0 = 0$ *and* $\beta_0 = 0$. The log-likelihood of the sampled cohort is a multinomial conditioned on the number of events n_i observed for individual *i* in the observation period [347]:

$$l(\alpha, \beta) = \sum_{ijk} n_{ijk} log \left[\frac{\exp(\alpha_j + \beta_k) e_{ijk}}{\sum_{rs} \exp(\alpha_r + \beta_s) e_{irs}} \right]$$

which cancels out the baseline incidence rate ϕ_i. The multinomial model can be fitted as a Poisson model with the number of events in the n_{ijk} as the response variable and the log of time spent in the interval $\ln(e_{ijk})$ as an offset, whose main effect model is as below:

$$n_{ijk} \sim Poisson(\lambda_{ijk} e_{ijk})$$

$$\log(\lambda_{ijk}) = \phi_i + \alpha_j + \beta_k$$

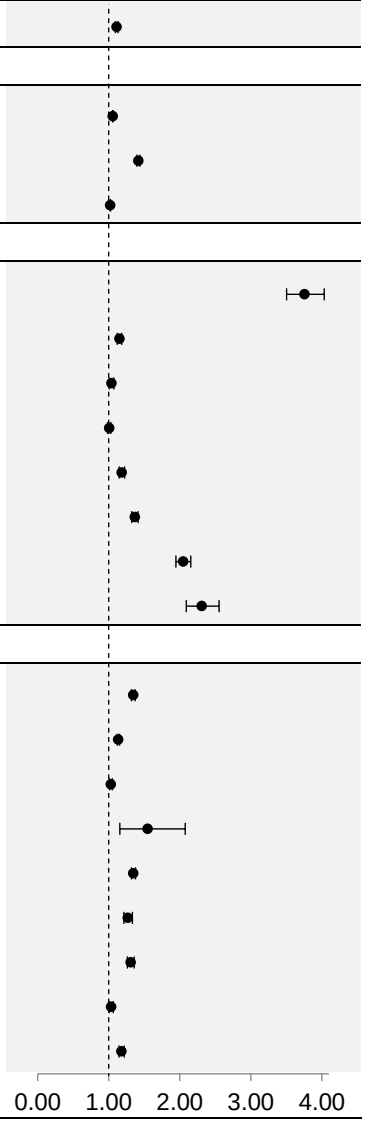
Maximum likelihood estimation is applied to estimate the incidence rate ratio for age (α) and exposure to risk (β). The observation period can be cut into smaller pieces by other time-varying variables like the season or the onset of a new disease. Extra variables could be fitted in the same way as age or risk in the above formula to estimate the incidence rate ratio in a fixed-effect Poisson regression conditioned on individuals.

Appendix 6. Result tables for Chapter 7

Result tables for the primary analyses of the Cox models

(a) The association between fracture hospitalisation and gabapentinoid exposure

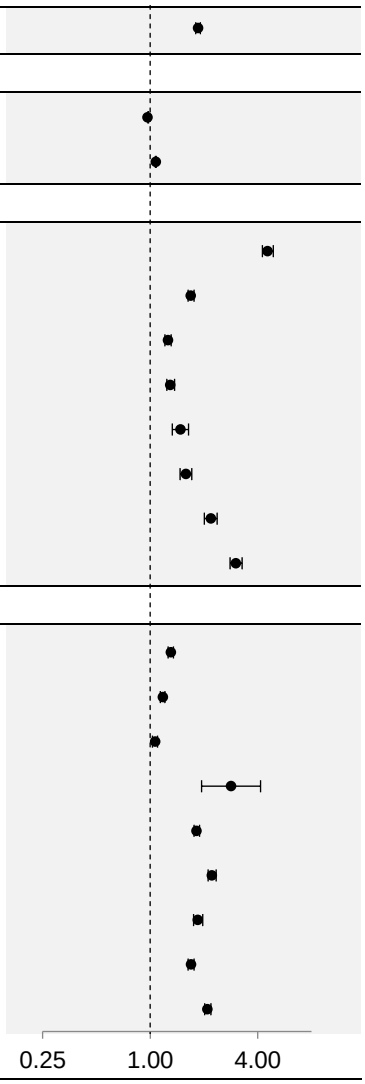
	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Exposure to gabapentinoids			
Gabapentinoids	1.42 (1.40, 1.44)*	1.11 (1.09, 1.13)*	
Baseline demographics			
Age	1.06 (1.06, 1.06)*	1.06 (1.06, 1.06)*	
Gender	1.54 (1.51, 1.56)*	1.42 (1.40, 1.44)*	
IMD	1.00 (1.00, 1.01)*	1.02 (1.02, 1.03)*	
Baseline comorbidities			
Alcohol use problem	3.46 (3.23, 3.70)*	3.76 (3.50, 4.03)*	
Depression	1.22 (1.19, 1.25)*	1.15 (1.12, 1.18)*	
Anxiety	1.13 (1.10, 1.16)*	1.04 (1.01, 1.07)*	
Diabetes	1.58 (1.54, 1.61)*	1.01 (0.98, 1.03)	
CKD	2.88 (2.79, 2.98)*	1.18 (1.15, 1.22)	
COPD	2.61 (2.52, 2.69)*	1.37 (1.32, 1.41)	
Epilepsy	2.04 (1.94, 2.14)*	2.05 (1.95, 2.16)	
Substance misuse	1.95 (1.77, 2.14)*	2.31 (2.09, 2.55)	
Baseline pain medication use			
Strong opioids	1.87 (1.84, 1.90)*	1.35 (1.32, 1.37)	
Weak opioids	1.68 (1.66, 1.70)*	1.14 (1.12, 1.15)	
TCAs	1.42 (1.40, 1.45)*	1.03 (1.01, 1.05)	
MAOIs	2.61 (1.95, 3.50)*	1.55 (1.16, 2.08)	
SSRIs	1.38 (1.35, 1.40)*	1.35 (1.32, 1.38)	
SNRIs	1.43 (1.37, 1.50)*	1.27 (1.21, 1.33)	
Hypnotics	2.59 (2.50, 2.69)*	1.31 (1.26, 1.36)	
Anxiolytics	1.29 (1.26, 1.33)*	1.03 (1.01, 1.06)	
Z-drugs	1.69 (1.64, 1.74)*	1.18 (1.15, 1.22)	



*Note: (1) HR: crude hazard ratio, aHR: adjusted hazard ratio; (2) * indicates a P value lower than 0.05*

(b) The association between suicide hospitalisation and gabapentinoid exposure

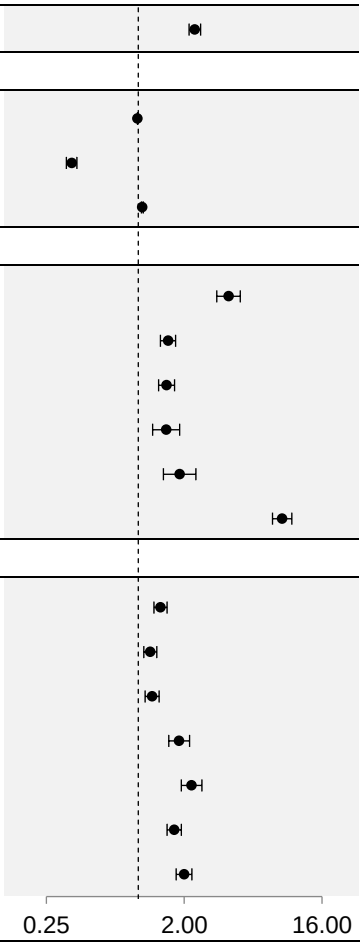
	CHR (95% CI)	aCHR (95% CI)	aCHR (95% CI)
Exposure to gabapentinoids			
Gabapentinoids	3.15 (3.07, 3.23)*	1.86 (1.80, 1.91)*	
Baseline demographics			
Age	0.97 (0.97, 0.97)*	0.97 (0.97, 0.98)*	
IMD	1.13 (1.12, 1.13)*	1.08 (1.07, 1.08)*	
Baseline comorbidities			
Alcohol use problem	14.54 (13.60, 15.53)*	4.56 (4.25, 4.89)*	
Depression	5.00 (4.85, 5.14)*	1.69 (1.63, 1.76)*	
Anxiety	3.87 (3.73, 4.01)*	1.26 (1.21, 1.31)*	
Diabetes	1.27 (1.21, 1.33)*	1.30 (1.24, 1.37)*	
CKD	1.03 (0.93, 1.14)*	1.48 (1.33, 1.64)*	
COPD	1.77 (1.65, 1.90)*	1.59 (1.47, 1.71)*	
Epilepsy	3.24 (2.98, 3.51)*	2.19 (2.01, 2.37)*	
Substance misuse	14.10 (13.13, 15.15)*	3.03 (2.80, 3.27)*	
Baseline pain medication use			
Strong opioids	2.90 (2.82, 3.00)*	1.31 (1.26, 1.35)*	
Weak opioids	1.96 (1.91, 2.01)*	1.18 (1.14, 1.21)*	
TCAs	2.10 (2.04, 2.17)*	1.07 (1.03, 1.10)*	
MAOIs	6.30 (4.32, 9.19)*	2.84 (1.94, 4.15)*	
SSRIs	3.98 (3.88, 4.09)*	1.82 (1.76, 1.89)*	
SNRIs	6.12 (5.84, 6.41)*	2.22 (2.11, 2.34)*	
Hypnotics	4.41 (4.16, 4.67)*	1.85 (1.75, 1.97)*	
Anxiolytics	4.28 (4.14, 4.42)*	1.70 (1.63, 1.76)*	
Z-drugs	5.49 (5.30, 5.69)*	2.10 (2.02, 2.19)*	



*Note: (1) CHR: crude cause-specific hazard ratio, aCHR: adjusted cause-specific hazard ratio; (2) * indicates a P value lower than 0.05*

(c) The association between suicide death and gabapentinoid exposure

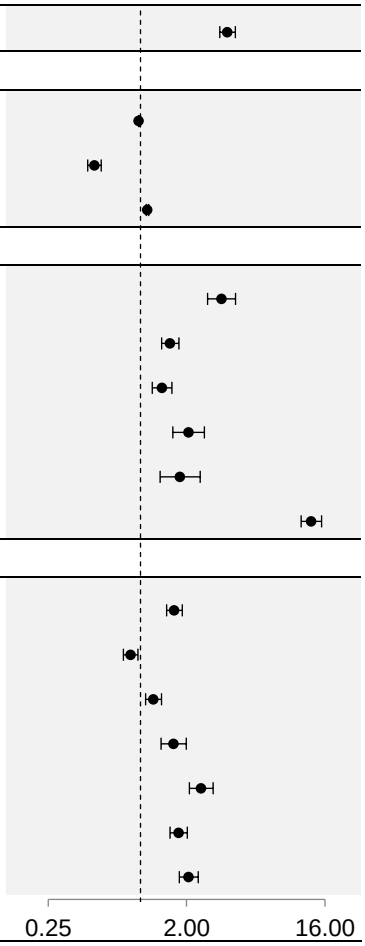
	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Exposure to gabapentinoids			
Gabapentinoids	3.98 (3.68, 4.29)*	2.35 (2.15, 2.56)*	
Baseline demographics			
Age	0.98 (0.98, 0.99)*	0.99 (0.99, 0.99)*	
Gender	0.38 (0.35, 0.41)*	0.37 (0.34, 0.40)*	
IMD	1.12 (1.10, 1.13)*	1.06 (1.05, 1.08)*	
Baseline comorbidities			
Alcohol use problem	21.36 (18.18, 25.10)*	3.90 (3.27, 4.66)*	
Depression	3.85 (3.52, 4.22)*	1.57 (1.40, 1.76)*	
Anxiety	3.83 (3.45, 4.26)*	1.53 (1.36, 1.73)*	
COPD	2.12 (1.73, 2.59)*	1.52 (1.24, 1.87)*	
Epilepsy	3.04 (2.38, 3.88)*	1.87 (1.46, 2.39)*	
Substance misuse	44.51 (39.23, 50.49)*	8.77 (7.58, 10.15)*	
Baseline pain medication use			
Strong opioids	3.45 (3.16, 3.76)*	1.40 (1.27, 1.54)*	
TCAs	2.30 (2.10, 2.51)*	1.20 (1.09, 1.32)*	
SSRIs	2.50 (2.29, 2.73)*	1.23 (1.11, 1.37)*	
SNRIs	5.16 (4.46, 5.98)*	1.85 (1.59, 2.17)*	
Hypnotics	5.82 (5.02, 6.74)*	2.24 (1.91, 2.61)*	
Anxiolytics	4.47 (4.07, 4.92)*	1.72 (1.54, 1.91)*	
Z-drugs	5.17 (4.63, 5.76)*	1.99 (1.77, 2.25)*	



*Note: (1) HR: crude hazard ratio, aHR: adjusted hazard ratio; (2) * indicates a P value lower than 0.05*

(d) The association between drug-related death and gabapentinoid exposure

	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Exposure to gabapentinoids			
Gabapentinoids	6.66 (6.02, 7.38)*	3.70 (3.29, 4.16)*	
Baseline demographics			
Age	0.97 (0.97, 0.97)*	0.98 (0.97, 0.98)*	
Gender	0.48 (0.43, 0.53)*	0.50 (0.45, 0.55)*	
IMD	1.19 (1.17, 1.21)*	1.11 (1.09, 1.13)*	
Baseline comorbidities			
Alcohol use problem	25.24 (20.81, 30.61)*	3.38 (2.74, 4.17)*	
Depression	4.49 (4.01, 5.03)*	1.57 (1.37, 1.78)*	
Anxiety	4.19 (3.67, 4.78)*	1.38 (1.19, 1.60)*	
COPD	2.69 (2.14, 3.39)*	2.06 (1.63, 2.61)*	
Epilepsy	3.38 (2.50, 4.56)*	1.81 (1.34, 2.45)*	
Substance misuse	81.42 (71.50, 92.71)*	13.03 (11.18, 15.20)*	
Baseline pain medication use			
Strong opioids	5.18 (4.67, 5.74)*	1.67 (1.48, 1.87)*	
Weak opioids	1.76 (1.59, 1.95)*	0.86 (0.77, 0.96)*	
TCAs	2.86 (2.56, 3.19)*	1.22 (1.08, 1.37)*	
SNRIs	5.84 (4.88, 6.99)*	1.65 (1.36, 1.99)*	
Hypnotics	7.94 (6.72, 9.39)*	2.49 (2.08, 2.98)*	
Anxiolytics	5.78 (5.16, 6.49)*	1.77 (1.56, 2.02)*	
Z-drugs	6.44 (5.66, 7.34)*	2.07 (1.79, 2.38)*	



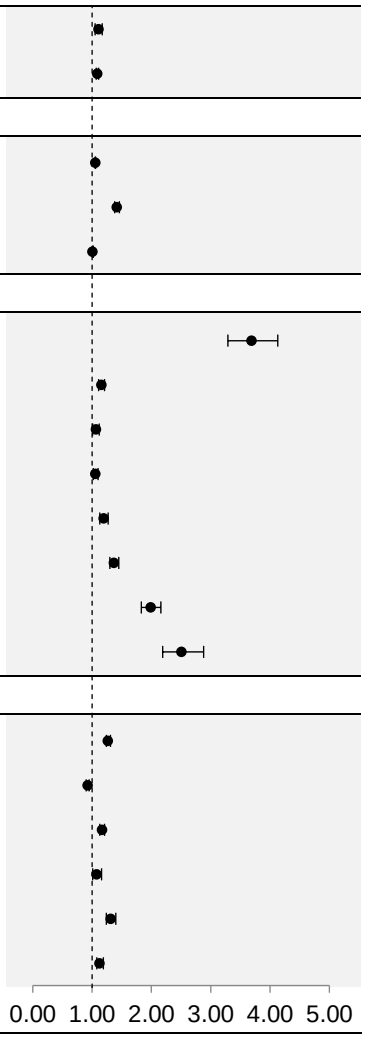
*Note: (1) HR: crude hazard ratio, aHR: adjusted hazard ratio; (2) * indicates a P value lower than 0.05*

Appendix 7. Result tables for Chapter 8

Result tables for the Cox models

(a) The association between fracture hospitalisation and high-dose gabapentinoid exposure

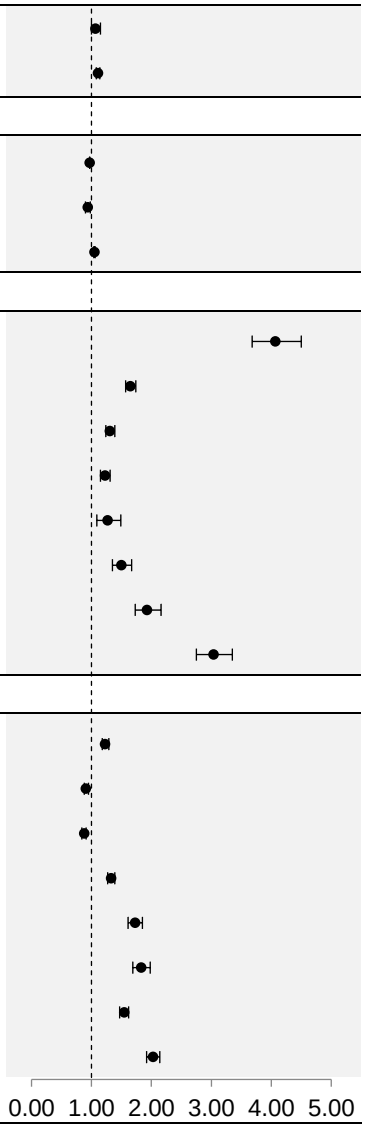
	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Exposure to gabapentinoids			
High dose exposure	1.09 (1.01, 1.17)*	1.11 (1.05, 1.17)*	
Persistent exposure	1.30 (1.27, 1.33)*	1.09 (1.07, 1.11)*	
Baseline demographics			
Age	1.05 (1.05, 1.05)*	1.06 (1.05, 1.06)*	
Gender	1.47 (1.43, 1.51)*	1.42 (1.38, 1.46)*	
IMD	0.98 (0.98, 0.99)*	1.01 (1.01, 1.02)*	
Baseline comorbidities			
Alcohol use problem	2.93 (2.63, 3.26)*	3.69 (3.29, 4.13)*	
Depression	1.00 (0.96, 1.04)*	1.16 (1.11, 1.21)*	
Anxiety	0.97 (0.92, 1.02)*	1.07 (1.01, 1.12)*	
Diabetes	1.39 (1.34, 1.44)*	1.06 (1.02, 1.10)*	
CKD	2.48 (2.34, 2.63)*	1.20 (1.13, 1.27)*	
COPD	2.17 (2.05, 2.29)*	1.37 (1.30, 1.45)*	
Epilepsy	1.66 (1.52, 1.80)*	1.99 (1.83, 2.16)*	
Substance misuse	1.68 (1.47, 1.91)*	2.51 (2.19, 2.88)*	
Baseline pain medication use			
Strong opioids	1.32 (1.28, 1.35)*	1.27 (1.24, 1.31)*	
TCAs	0.94 (0.92, 0.97)*	0.93 (0.90, 0.95)*	
SSRIs	1.06 (1.03, 1.10)*	1.17 (1.13, 1.21)*	
SNRIs	1.00 (0.94, 1.07)*	1.08 (1.01, 1.16)*	
Hypnotics	1.97 (1.86, 2.09)*	1.32 (1.24, 1.40)*	
Z-drugs	1.29 (1.23, 1.35)*	1.13 (1.08, 1.19)*	



*Note: (1) HR: crude hazard ratio, aHR: adjusted hazard ratio; (2) * indicates a P value lower than 0.05*

(b) The association between suicide hospitalisation and high-dose gabapentinoid exposure

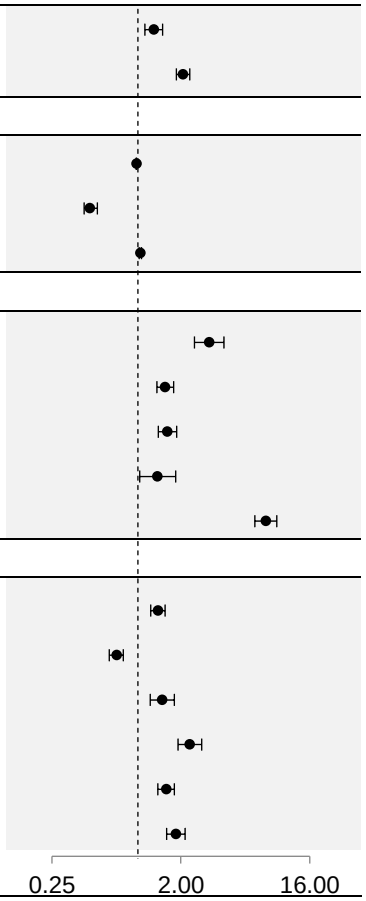
	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Exposure to gabapentinoids			
High dose exposure	3.79 (3.54, 4.05)*	1.07 (1.00, 1.15)*	
Persistent exposure	2.18 (2.10, 2.27)*	1.11 (1.08, 1.14)*	
Baseline demographics			
Age	0.97 (0.97, 0.97)*	0.97 (0.97, 0.97)*	
Gender	0.97 (0.94, 1.01)	0.94 (0.90, 0.98)*	
IMD	1.09 (1.08, 1.10)*	1.05 (1.04, 1.06)*	
Baseline comorbidities			
Alcohol use problem	9.60 (8.74, 10.55)*	4.07 (3.68, 4.50)*	
Depression	3.24 (3.11, 3.38)*	1.65 (1.57, 1.74)*	
Anxiety	2.86 (2.72, 3.00)*	1.31 (1.24, 1.39)*	
Diabetes	0.97 (0.90, 1.03)	1.23 (1.15, 1.31)*	
CKD	0.74 (0.63, 0.86)*	1.27 (1.09, 1.49)*	
COPD	1.27 (1.14, 1.40)*	1.50 (1.35, 1.67)*	
Epilepsy	2.38 (2.13, 2.65)*	1.93 (1.73, 2.16)*	
Substance misuse	8.84 (8.07, 9.69)*	3.04 (2.75, 3.35)*	
Baseline pain medication use			
Strong opioids	1.52 (1.46, 1.58)*	1.23 (1.18, 1.29)*	
Weak opioids	1.04 (1.00, 1.08)	0.91 (0.88, 0.95)*	
TCAs	0.95 (0.91, 0.99)*	0.88 (0.84, 0.91)*	
SSRIs	2.36 (2.27, 2.46)*	1.33 (1.27, 1.39)*	
SNRIs	3.11 (2.92, 3.31)*	1.73 (1.61, 1.85)*	
Hypnotics	2.77 (2.57, 3.00)*	1.83 (1.69, 1.98)*	
Anxiolytics	2.42 (2.32, 2.53)*	1.55 (1.47, 1.62)*	
Z-drugs	3.45 (3.28, 3.63)*	2.03 (1.92, 2.14)*	



*Note: (1) HR: crude hazard ratio, aHR: adjusted hazard ratio; (2) * indicates a P value lower than 0.05*

(c) The association between suicide death and high-dose gabapentinoid exposure

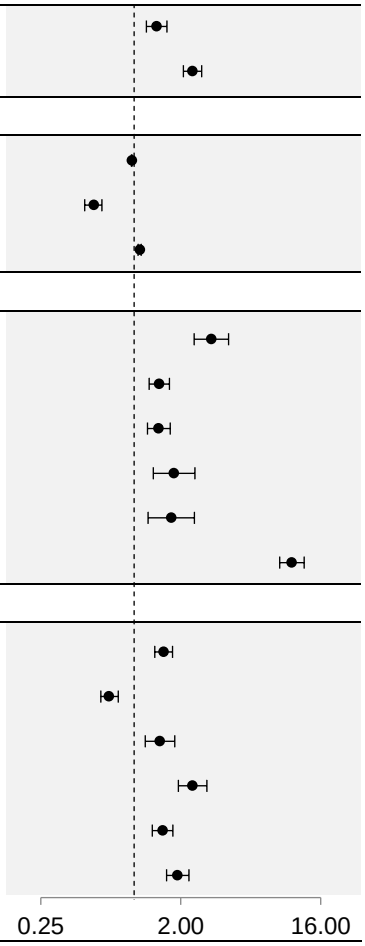
	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Exposure to gabapentinoids			
High dose exposure	4.84 (4.10, 5.71)*	1.29 (1.12, 1.49)*	
Persistent exposure	1.58 (1.42, 1.77)*	2.07 (1.86, 2.31)*	
Baseline demographics			
Age	0.97 (0.97, 0.97)*	0.98 (0.97, 0.98)*	
Gender	0.44 (0.40, 0.49)*	0.46 (0.42, 0.52)*	
IMD	1.09 (1.07, 1.12)*	1.04 (1.02, 1.06)*	
Baseline comorbidities			
Alcohol use problem	12.84 (10.28, 16.03)*	3.16 (2.49, 4.01)*	
Depression	2.91 (2.58, 3.27)*	1.55 (1.36, 1.78)*	
Anxiety	3.18 (2.78, 3.63)*	1.61 (1.39, 1.87)*	
COPD	1.29 (0.96, 1.72)	1.37 (1.03, 1.84)*	
Substance misuse	27.03 (23.11, 31.63)*	7.87 (6.60, 9.40)*	
Baseline pain medication use			
Strong opioids	1.76 (1.58, 1.97)*	1.38 (1.23, 1.55)*	
Weak opioids	0.77 (0.69, 0.86)*	0.71 (0.63, 0.79)*	
SNRIs	2.80 (2.33, 3.36)*	1.48 (1.22, 1.80)*	
Hypnotics	3.93 (3.27, 4.71)*	2.31 (1.91, 2.80)*	
Anxiolytics	2.54 (2.25, 2.87)*	1.58 (1.38, 1.80)*	
Z-drugs	3.30 (2.87, 3.80)*	1.85 (1.59, 2.14)*	



*Note: (1) HR: crude hazard ratio, aHR: adjusted hazard ratio; (2) * indicates a P value lower than 0.05*

(d) The association between drug-related death and high-dose gabapentinoid exposure

	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Exposure to gabapentinoids			
High dose exposure	6.22 (5.23, 7.40)*	1.40 (1.20, 1.63)*	
Persistent exposure	2.10 (1.85, 2.38)*	2.38 (2.08, 2.73)*	
Baseline demographics			
Age	0.96 (0.96, 0.96)*	0.97 (0.96, 0.97)*	
Gender	0.49 (0.44, 0.56)*	0.55 (0.48, 0.62)*	
IMD	1.15 (1.13, 1.18)*	1.09 (1.06, 1.11)*	
Baseline comorbidities			
Alcohol use problem	15.17 (11.95, 19.25)*	3.15 (2.44, 4.07)*	
Depression	2.97 (2.60, 3.41)*	1.45 (1.25, 1.69)*	
Anxiety	3.08 (2.64, 3.60)*	1.44 (1.22, 1.71)*	
COPD	1.59 (1.17, 2.15)*	1.81 (1.33, 2.47)*	
Epilepsy	2.44 (1.74, 3.44)*	1.74 (1.23, 2.45)*	
Substance misuse	39.77 (33.94, 46.61)*	10.43 (8.70, 12.51)*	
Baseline pain medication use			
Strong opioids	2.09 (1.84, 2.36)*	1.55 (1.36, 1.77)*	
Weak opioids	0.75 (0.66, 0.85)*	0.69 (0.61, 0.79)*	
SNRIs	2.91 (2.36, 3.58)*	1.47 (1.18, 1.83)*	
Hypnotics	4.41 (3.61, 5.39)*	2.38 (1.93, 2.95)*	
Anxiolytics	2.68 (2.33, 3.07)*	1.53 (1.31, 1.78)*	
Z-drugs	3.64 (3.11, 4.25)*	1.91 (1.62, 2.26)*	



*Note: (1) HR: crude hazard ratio, aHR: adjusted hazard ratio; (2) * indicates a P value lower than 0.05*

Appendix 8. Result tables for Chapter 9

Result table for the primary SCCS analysis

Covariates	Incidence Rate Ratio	adjusted Incidence Rate Ratio
Gabapentinoid exposure episode (reference group: baseline period)		
1-7 days	1.64 (1.49, 1.80)	1.36 (1.24, 1.50)
8-14 days	1.35 (1.22, 1.50)	1.13 (1.01, 1.25)
15-28 days	1.17 (1.07, 1.27)	0.97 (0.89, 1.06)
29+ days	1.17 (1.14, 1.21)	0.84 (0.82, 0.87)
Age (reference group: age 18)		
Age 19	0.81 (0.45, 1.44)	0.80 (0.45, 1.44)
Age 20	0.76 (0.43, 1.34)	0.76 (0.43, 1.34)
Age 21	0.92 (0.53, 1.58)	0.91 (0.53, 1.58)
Age 22	0.84 (0.49, 1.45)	0.84 (0.48, 1.44)
Age 23	0.80 (0.46, 1.38)	0.79 (0.46, 1.37)
Age 24	0.85 (0.49, 1.46)	0.84 (0.49, 1.45)
Age 25	0.75 (0.44, 1.31)	0.75 (0.43, 1.29)
Age 26	0.76 (0.44, 1.31)	0.75 (0.43, 1.30)
Age 27	0.62 (0.36, 1.08)	0.61 (0.35, 1.06)
Age 28	0.70 (0.40, 1.21)	0.69 (0.40, 1.20)
Age 29	0.79 (0.46, 1.37)	0.78 (0.45, 1.35)
Age 30	0.73 (0.42, 1.27)	0.73 (0.42, 1.26)
Age 31	0.74 (0.42, 1.28)	0.73 (0.42, 1.26)
Age 32	0.76 (0.44, 1.32)	0.75 (0.43, 1.31)
Age 33	0.77 (0.45, 1.34)	0.77 (0.44, 1.33)
Age 34	0.65 (0.37, 1.13)	0.64 (0.37, 1.12)
Age 35	0.74 (0.42, 1.28)	0.73 (0.42, 1.27)
Age 36	0.75 (0.43, 1.32)	0.75 (0.43, 1.31)
Age 37	0.72 (0.41, 1.25)	0.71 (0.41, 1.25)
Age 38	0.76 (0.43, 1.32)	0.75 (0.43, 1.31)
Age 39	0.78 (0.45, 1.37)	0.78 (0.45, 1.37)
Age 40	0.80 (0.46, 1.40)	0.80 (0.46, 1.40)
Age 41	0.75 (0.43, 1.32)	0.75 (0.43, 1.32)
Age 42	0.82 (0.47, 1.43)	0.82 (0.47, 1.43)
Age 43	0.83 (0.47, 1.45)	0.83 (0.48, 1.46)
Age 44	0.75 (0.43, 1.31)	0.76 (0.43, 1.32)
Age 45	0.82 (0.47, 1.43)	0.83 (0.47, 1.45)
Age 46	0.87 (0.50, 1.53)	0.89 (0.51, 1.55)
Age 47	0.90 (0.52, 1.58)	0.92 (0.52, 1.61)
Age 48	0.93 (0.53, 1.62)	0.95 (0.54, 1.66)

Age 49	0.96 (0.55, 1.68)	0.98 (0.56, 1.72)
Age 50	1.06 (0.61, 1.87)	1.10 (0.63, 1.92)
Age 51	1.06 (0.60, 1.85)	1.10 (0.62, 1.92)
Age 52	1.16 (0.66, 2.04)	1.22 (0.69, 2.14)
Age 53	1.22 (0.69, 2.14)	1.29 (0.73, 2.26)
Age 54	1.24 (0.71, 2.18)	1.32 (0.75, 2.32)
Age 55	1.36 (0.78, 2.40)	1.47 (0.83, 2.58)
Age 56	1.60 (0.91, 2.80)	1.73 (0.99, 3.04)
Age 57	1.50 (0.85, 2.63)	1.64 (0.93, 2.88)
Age 58	1.62 (0.92, 2.84)	1.79 (1.02, 3.15)
Age 59	1.95 (1.11, 3.43)	2.19 (1.24, 3.85)
Age 60	1.87 (1.06, 3.29)	2.11 (1.20, 3.72)
Age 61	2.14 (1.22, 3.77)	2.45 (1.39, 4.32)
Age 62	2.19 (1.24, 3.86)	2.53 (1.44, 4.47)
Age 63	2.47 (1.40, 4.36)	2.91 (1.65, 5.13)
Age 64	2.61 (1.48, 4.60)	3.10 (1.76, 5.48)
Age 65	2.85 (1.61, 5.02)	3.43 (1.94, 6.06)
Age 66	3.12 (1.77, 5.51)	3.82 (2.16, 6.74)
Age 67	3.55 (2.01, 6.26)	4.39 (2.49, 7.76)
Age 68	3.94 (2.24, 6.96)	4.96 (2.81, 8.78)
Age 69	4.30 (2.44, 7.60)	5.51 (3.12, 9.75)
Age 70	5.29 (3.00, 9.33)	6.88 (3.89, 12.17)
Age 71	5.36 (3.03, 9.46)	7.08 (4.00, 12.54)
Age 72	6.61 (3.74, 11.67)	8.89 (5.02, 15.75)
Age 73	7.27 (4.11, 12.84)	9.94 (5.61, 17.61)
Age 74	8.55 (4.84, 15.11)	11.92 (6.72, 21.13)
Age 75	9.68 (5.47, 17.10)	13.78 (7.77, 24.44)
Age 76	10.98 (6.21, 19.41)	15.97 (9.00, 28.34)
Age 77	13.65 (7.72, 24.14)	20.27 (11.42, 35.98)
Age 78	16.58 (9.38, 29.33)	25.16 (14.16, 44.68)
Age 79	18.94 (10.70, 33.51)	29.40 (16.55, 52.26)
Age 80	21.30 (12.04, 37.71)	33.79 (19.00, 60.10)
Age 81	27.57 (15.57, 48.80)	44.84 (25.20, 79.78)
Age 82	34.08 (19.24, 60.34)	56.83 (31.92, 101.17)
Age 83	41.16 (23.23, 72.92)	70.26 (39.43, 125.18)
Age 84	49.50 (27.93, 87.74)	86.44 (48.48, 154.14)
Age 85	63.30 (35.70, 112.24)	113.21 (63.44, 202.01)
Age 86	72.92 (41.10, 129.40)	133.36 (74.66, 238.23)
Age 87	84.21 (47.41, 149.56)	158.08 (88.38, 282.75)
Age 88	110.00 (61.90, 195.49)	211.30 (118.02, 378.29)
Age 89	134.54 (75.62, 239.36)	264.78 (147.68, 474.74)

Age 90	160.86 (90.28, 286.61)	325.92 (181.44, 585.46)
Age 91	196.47 (110.05, 350.76)	407.91 (226.55, 734.44)
Age 92	251.49 (140.56, 449.99)	533.89 (295.76, 963.75)
Age 93	295.21 (164.45, 529.96)	641.18 (353.91, 1161.63)
Age 94	361.20 (200.26, 651.48)	804.68 (441.92, 1465.21)
Age 95	493.89 (272.36, 895.59)	1117.54 (610.28, 2046.43)
Age 96	556.51 (303.48, 1020.50)	1287.14 (694.99, 2383.83)
Age 97	798.59 (431.42, 1478.24)	1880.29 (1005.54, 3515.99)
Age 98	838.57 (442.65, 1588.60)	2018.81 (1055.07, 3862.88)
Age 99	1044.86 (536.02, 2036.71)	2590.68 (1315.80, 5100.80)
Age 100	1103.32 (534.37, 2278.03)	2872.90 (1377.55, 5991.48)
Age 101	817.88 (340.65, 1963.73)	2163.54 (893.07, 5241.33)
Age 102	928.19 (344.42, 2501.42)	2529.66 (933.16, 6857.58)
Age 103	2061.99 (730.11, 5823.48)	5693.31 (2005.92, 16159.06)
Age 104	0.00 (0.00, .)	0.01 (0.00, .)
Age 105	0.00 (0.00, .)	0.01 (0.00, .)
Age 106	0.00 (0.00, .)	0.01 (0.00, .)
Age 107	0.00 (0.00, .)	0.01 (0.00, .)
Season (reference group: winter)		
Spring	0.99 (0.96, 1.01)	0.98 (0.95, 1.00)
Summer	1.01 (0.98, 1.03)	1.02 (1.00, 1.05)
Autumn	0.96 (0.94, 0.99)	1.00 (0.98, 1.03)
Diseases (reference group: disease-free period)		
Osteoporosis	1.53 (1.47, 1.59)	0.67 (0.64, 0.70)
Rheumatoid arthritis	2.34 (2.09, 2.62)	1.27 (1.13, 1.43)
Drug exposure (reference group: exposure-free period)		
Fracture related drug exposure	1.29 (1.25, 1.32)	1.15 (1.12, 1.18)

Number of fracture hospitalisation cases and follow up time in each risk period

	Fractures (n)	Follow-up time (person-year)
Primary analysis		
Baseline period	38,477	332,893
1-7 days	435	1,882
8-14 days	350	1,841
15-28 days	563	3,441
29+ days	9,627	64,100
Subgroup analysis		
Drug		
Gabapentin		
Baseline period	22,429	192,779
1-7 days	253	948
8-14 days	188	920
15-28 days	292	1,705
29+ days	4,637	29,876
Pregablin		
Baseline period	9,212	75,539
1-7 days	98	394
8-14 days	90	390
15-28 days	147	739
29+ days	2,563	16,021
Gender		
Female		
Baseline period	26,548	232,605
1-7 days	330	1,305
8-14 days	249	1,277
15-28 days	407	2,384
29+ days	7,003	44,694
Male		
Baseline period	11,929	100,289
1-7 days	105	577
8-14 days	101	564
15-28 days	156	1,057
29+ days	2,624	19,406
Sensitivity analysis		
Analysis 1: include a 28-day pre-exposure period		
Baseline period	36,508	325,254
Pre-exposure period	1,941	7,373
1-7 days	415	1,880

8-14 days	351	1,844
15-28 days	572	3,444
29+ days	9,665	64,363
Analysis 2: include a 90-day pre-exposure period		
Baseline period	32,945	313,842
Pre-exposure period	5,504	18,785
1-7 days	415	1,880
8-14 days	351	1,844
15-28 days	572	3,444
29+ days	9,665	64,363
Analysis 3: separate the first exposures from subsequent exposures		
Baseline period	38,477	332,893
First exposure		
1-7 days	233	774
8-14 days	175	758
15-28 days	307	1,421
29+ days	4,622	29,376
Subsequent exposures		
1-7 days	202	1,108
8-14 days	175	1,083
15-28 days	256	2,020
29+ days	5,005	34,724
Analysis 4: separate high-dose exposures from low-dose exposures		
Baseline period	38,477	332,893
Non-high-dose		
1-7 days	435	1,879
8-14 days	350	1,838
15-28 days	563	3,431
29+ days	9,541	63,784
High-dose		
1-7 days	0	3
8-14 days	0	3
15-28 days	0	10
29+ days	86	316
Analysis 5: move the osteoporosis diagnosis 1 year earlier		
Baseline period	22,429	192,779
1-7 days	253	948
8-14 days	188	920
15-28 days	292	1,705
29+ days	4,637	29,876

Analysis 6: include only the first fracture hospitalisation of each patient		
Baseline period	31,917	332,893
1-7 days	363	1,882
8-14 days	282	1,841
15-28 days	442	3,441
29+ days	7,513	64,100