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GABAPENTINOID USE, RISKS, AND THE IMPACT OF RECLASSIFICATION FOR CHRONIC PAIN PATIENTS IN THE UNITED KINGDOM

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I. Abstract

Background: Chronic pain is a significant health concern in the UK, leading to increased use of pregabalin and gabapentin beyond their original indications for epilepsy, anxiety, and neuropathic pain. This expanded, often unlicensed use has raised concerns due to limited efficacy evidence and misuse risks, especially with opioids. Consequently, gabapentinoids were reclassified as Schedule III controlled drugs in the UK in 2019. This study utilised CPRD data to examine gabapentinoid prescribing patterns from January 2005 to December 2020 and assessed the impact of reclassification on prescribing trends, focusing on chronic pain patients. Moreover, it explored the association between gabapentinoid use and harms from August 2012 to July 2020.

Methods: This study employed pharmacoepidemiological approaches, comprising a repeated cross-sectional analysis to examine prescribing patterns in chronic pain patients, an interrupted time series to assess the impact of gabapentinoid reclassification, and a cohort study to investigate the association with overdose and mortality.

Results: There was a significant increase in gabapentinoid prescriptions in a cohort of 415,179 people with chronic pain. The prevalence of gabapentin and pregabalin users escalated from 38.8 to 125, and from 12.8 to 108.9 per 10,000 registrants, respectively. Incidence rates of new users also surged, with gabapentin increasing from 13.8 to 49.7, and pregabalin from 8 to 38.5 per 10,000 registrants. Over 60% of prescriptions were for unlicensed indications, primarily chronic back pain, while nearly 20% were for licensed uses. The reclassification of gabapentinoids resulted in a 13% and 18% decrease in the monthly prevalence of pregabalin and gabapentin users per 10,000 registrants,

respectively. Time-varying analysis showed a significant association between current gabapentinoid use and harms, with hazard ratios (HRs) of 1.61 and 1.57 for overdose, and 1.19 and 1.12 for all-cause mortality, for gabapentin and pregabalin, respectively.

Conclusion: There was a significant rise in gabapentinoid prescriptions for chronic pain from 2005 to 2020, notably for unlicensed purposes. Reclassification led to a reduction in both gabapentinoid users and doses. Significant associations between gabapentinoid use and increased overdose and mortality risks were also identified. These findings inform policy and prescribing guidelines for safer gabapentinoid use in chronic pain patients, highlighting the need for targeted misuse prevention and intervention programmes.

II. Acknowledgement

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A&E	Accident and Emergency
ACMD	Advisory Council on the Misuse of Drugs
ADD	Average daily dose
ADHD	Attention-Deficit Hyperactivity Disorder
ADRs	Adverse Drug Reactions
AEDs	Anti-epileptic drugs
AEs	Adverse effects
AMT	Amitriptyline
APC	Admitted Patient Care
BPS	British Pain Society
CAM	Complementary and Alternative Medicine
CBT	Cognitive-Behavioral Therapy
CHD	Coronary Heart Disease
CI	Confidence Interval
CNCP	Chronic Non-Cancer Pain
CP	Chronic pain
CPRD	Clinical Practice Research Datalink
crd	Current registration date
DDD	Defined Daily Dose
DLX	Duloxetine
DMARDs	Disease-Modifying AntiRheumatic Drugs
DRD	Drug-related death
DS	Days' supply
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
frd	First registration date
GABA	Gamma-aminobutyric acid
GBP	Gabapentin
GEn	Gabapentin enacarbil
GP	General Practice
EHR	Electronic Health Records
HES	Hospital Episode Statistics
HIT	Headache Impact Test
ICD-10	International Classification of Diseases, version 10
IDO	Intentional drug overdose
IMD	Index of Multiple Deprivation
INPS	In Practice Systems Ltd.
ISAC	Independent Scientific Advisory Committee
ITS	Interrupted time series
LBP	Lower Back Pain
MA	Meta-analyses
MCCD	Medical Certificate of Cause of Death

MI	myocardial infarction
NBHW	National Board of Health and Welfare
ndd	Numeric Daily Doses
NDTMS	National Drug Treatment Monitoring System
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRC	National Rehabilitation Centre
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OMT	Opioid Maintenance Therapy
ONS	Office for National Statistics
OUD	Opioid Use Disorder
Patid	Patient identifier
PDD	Prescribed daily dose
pDPN	Painful Diabetic Peripheral Neuropathy
PGB	Pregabalin
PhD	Doctor of Philosophy
PHE	Public Health England
PHN	Postherpetic Neuralgia
QOF	Quality and Outcome Framework
QOL	Quality Of Life
QTY	Quantity
RA	Rheumatoid Arthritis
RCTs	Randomised Control Trials
RON	Registration Online
SEs	Side effects
SFDA	Saudi Food and Drug Authority's
SIGN	Scottish Intercollegiate Guidelines Network
SUD	Substance Use Disorder
UAE	United Arab Emirates
UK	United Kingdom
US	United States
UTS	Up-to-standard
VAS	Visual Analogue Scale
VIF	variance inflation factor
WHO	World Health Organisation
WOMAC	Western Ontario and McMaster
yob	Year of birth

Chapter 1: Introduction and literature review

This chapter offers a comprehensive overview of chronic non-cancer pain (CNCP), addressing its definition, the diverse types, and the management approaches. It specifically focuses on the role of gabapentinoids, such as pregabalin and gabapentin, in managing CNCP, provides a review of the available evidence concerning gabapentinoids prescribing trends, the safety concerns associated with their usage, and the effects of reclassifying them as controlled substances.

1.1 Search Strategy

The methodology for this narrative review involved an extensive search across various databases such as PubMed, Google Scholar, the Cochrane Library, Embase, Medline, and the University of Nottingham library search database. It covered articles published from January 2000 and continued as an ongoing process throughout the duration of the PhD. The search utilised both free text and keywords to identify relevant studies. Keywords used in this search included terms such as pregabalin, gabapentin, pain, chronic pain, CNCP, neuropathic pain, back pain, fibromyalgia, musculoskeletal pain, Osteoarthritis (OA), joint pain, headache, migraine, reclassification of gabapentinoid, abuse, overuse, overdose, mortality, and death. Synonymous terms were also employed to maximise the retrieval of references. Following the search and subsequent removal of duplicates, the abstracts and full articles underwent review to ensure that the selected publications addressed the pertinent issues or queries. Non-human, non-English, and paediatric articles were excluded from the search.

1.2 Overview of chronic non cancer pain

1.2.1 Definition of chronic non-cancer pain

CNCP is pain lasting beyond typical tissue healing, often considered chronic after three months (Wong, 2022; WHO, 2015). Both the British Pain Society (BPS) and the Scottish Intercollegiate Guidelines Network (SIGN) use this three-month guideline (BPS, 2012; SIGN, 2019). CNCP arises from repeated nociceptor stimulation or alteration due to tissue damage from injuries, illnesses, or damage to the nervous system (Turk et al., 2011).

1.2.2 Types of pain

Pain has been classified into neuropathic and nociceptive pain (Baron et al., 2010). Moreover, a new category called 'nociplastic pain' was established by the International Association on the Study of Pain (IASP) in 2017 (Kosek et al., 2021; Bentley et al., 2018). According to the IASP (2020), neuropathic pain is persistent pain that arises from a lesion or illness affecting the somatosensory nerve system. The pain may occur without any apparent cause or might be triggered by a painful stimulus (hyperalgesia) or by a typically non-painful stimulus that causes pain (allodynia) (IASP, 2020). The symptoms include hyperalgesia, sudden pain, and paresthesia (Truini and Cruccu, 2006). Common conditions include trigeminal neuralgia, post-herpetic neuralgia, pain from peripheral nerve injury, diabetic neuropathy, and pain after a central stroke (Bentley et al., 2018). However, nociceptive pain is caused by the activation of nociceptors due to tissue damage. It may be somatic or visceral, affecting joints, muscles, and tendons (Aronoff, 2016; Armstrong and Herr, 2019). Nociplastic pain is caused by altered nociception, occurring without physical damage that activates peripheral nociceptors, or resulting from disease or abnormalities in the

somatosensory system (Kosek et al., 2021). It can be characterised as pain that lasts at least three months, is region-specific, is neither nociceptive nor neuropathic, and increases local sensitivity (Kosek et al., 2021). Examples of nociplastic pain include fibromyalgia, non-specific low back pain, tension headaches, and persistent migraines (Fitzcharles et al., 2021; Murphy, 2023).

1.2.3 Management of chronic non cancer pain

CNCP is a leading contributor to global suffering and disability, primarily due to the challenges associated with its management (Wong, 2022; BMA, 2017). In order to effectively manage chronic pain, it is often necessary to provide patients with pharmacological treatment in addition to non-pharmacological interventions (Chang et al., 2015). Non-pharmacological treatments include psychoeducational approaches (e.g. cognitive-behavioural therapy (CBT), family therapy, psychotherapy, complementary and alternative medicine (CAM) approaches), physical therapy, and patient education (Skelly et al., 2018).

The selection of pharmacological treatment for chronic pain depends on its type (Kela et al., 2021). Distinguishing between neuropathic, nociceptive, and nociplastic pain is crucial due to their differing treatments (Kela et al., 2021). Treatment guidelines recommend analgesics, including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and short-term use of opioids, for nociceptive conditions such as tendinitis, OA, and arthritis, as well as for non-specific chronic back pain (NICE, 2014; SIGN, 2019). Antidepressants, such as amitriptyline (AMT) and duloxetine (DLX), and anti-epileptic drugs (AEDs), including gabapentin (GBP) and pregabalin (PGB), are recommended for treating neuropathic pain conditions (NICE, 2013). The Food and Drug Administration (FDA) has approved medications for treating nociplastic pain

conditions, such as fibromyalgia (FM), including pregabalin, DLX, and milnacipran (Fitzcharles et al., 2021). In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) and the SIGN have recommended antidepressants for the treatment of nociplastic pain (NICE, 2021a; SIGN, 2019).

1.3 Overview of pregabalin and gabapentin and their role in chronic pain management

1.3.1 Pregabalin and gabapentin medications and chronic pain (Historical Perspective)

GBP and PGB, as GABA (gamma-aminobutyric acid) mimic drugs, are primarily used for epilepsy treatment. Their efficacy extends to analgesic and anxiolytic effects (Abou-Khalil, 2019).

GBP was originally developed as a muscle relaxant and antispasmodic medication. Subsequently, its anticonvulsive effects were discovered then its use expanded to analgesic applications for diverse neuropathic and non-neuropathic pain conditions (Lumsden et al., 2019; Rocha et al., 2019). In the UK, GBP was licensed for epilepsy in 1993 and for neuropathic conditions like postherpetic neuralgia (PHN) later on (Bennett and Simpson, 2004). The European Medicines Agency (EMA) approved it for peripheral neuropathic pain in 2001(EMA, 2006; Ludwig et al., 2021). In the United States (US), GBP is approved for PHN and used off-label for a range of conditions including restless leg syndrome, migraine, bipolar disorder, anxiety, and alcohol withdrawal (Ziganshina et al., 2017; Goodman and Brett, 2019b; Yasaei et al., 2022).

By 2004, PGB had received approval in several countries for neuropathic pain treatment, including for diabetic neuropathy (DN), PHN, and resistant partial epilepsy in the UK, as well as for generalised anxiety disorder (Wettermark et al., 2014). The

EMA authorised its use for both peripheral and central neuropathic pain (EMA, 2018; Ludwig et al., 2021), while in the US, its applications extended to peripheral DN, spinal cord injury (SCI), PHN, as an adjunct therapy for focal seizures, and FM, with the latter condition approved in 2007 (Derry et al., 2016; Goodman and Brett, 2019b).

1.3.2 Analgesic mechanism of action of gabapentin and pregabalin

The mechanisms of action for both PGB and GBP are similar, primarily involving the inhibition of certain neurotransmitters to achieve their analgesic effects. Within the central nervous system, both drugs bind to voltage-gated calcium channels, specifically the alpha-2-delta subunit of these channels. This binding does not block the channels but reduces the influx of calcium ions. This reduction in calcium influx is significant because it diminishes the release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P, which are involved in the transmission of pain signals and epileptic activity. By reducing neurotransmitter release, pregabalin and gabapentin decrease the excitability of nerve cells, leading to a reduction in pain perception. This mechanism is particularly relevant in conditions like neuropathic pain, where abnormal neuronal excitability plays a key role (Chincholkar, 2020). Figure 1-1 illustrates the mechanism of action of the analgesic effect of gabapentinoids.

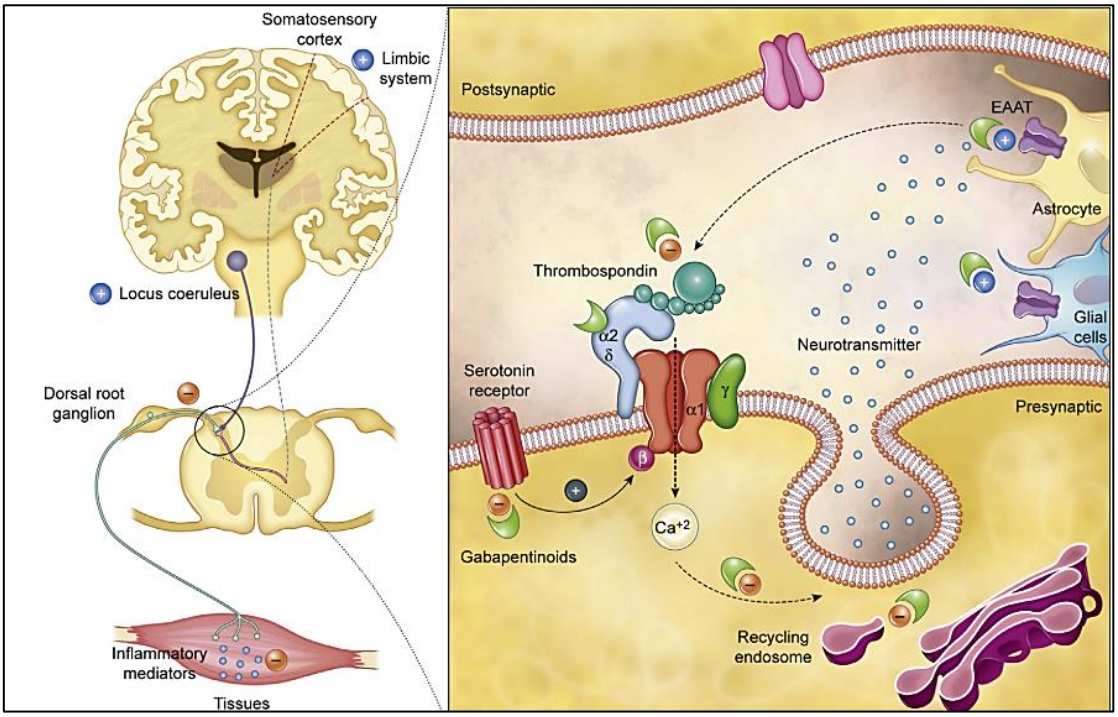


Figure 1-1: Mechanism of Action of Analgesic Effect of Gabapentinoids

Note: Adapted from Chincholkar, 2020. "Gabapentinoids: Pharmacokinetics, Pharmacodynamics and Considerations for Clinical Practice." British Journal of Pain, vol. 14, no. 2, pp. 104–114. Copyright © 2020 The British Pain Society. DOI: 10.1177/2049463720912496. Reused with permission from SAGE Publications: https://us.sagepub.com/en-us/nam/pre-approved-permission-requests-journals.

1.3.3 Efficacy and tolerability of pregabalin and gabapentin in managing chronic non-cancer pain

1.3.3.1 The efficacy and tolerability of gabapentin and pregabalin utilisation in the management of neuropathic pain

Neuropathic pain originates from abnormalities or impairments in the somatosensory system, including peripheral nerves, spinal cord, or brain (IASP, 2020; Campbell and Meyer, 2006). It is often characterised as burning, shooting, or tingling (Sommer et al., 2018). This type of pain can profoundly impact patients, leading to significant discomfort, sleep disturbances, and a decrease in overall quality of life (QOL) (Finnerup et al., 2021; Ferini-Strambi, 2017). It can be the result of various conditions,

such as diabetes (diabetic neuropathy), stroke, shingles (postherpetic neuralgia), multiple sclerosis, and spinal cord injury (Bentley et al. 2018).

The prevalence of neuropathic pain varies depending on its cause and the demographic studied, and it is widely recognised as a common condition. Diabetic neuropathy, for example, affects about 20% to 30% of individuals with diabetes (Davies et al., 2006; Abbott et al., 2011; Bouhassira et al., 2013; Aslam et al., 2015), and this figure may rise to as much as 50% within the same population (Pop-Busui et al., 2016). In the United States, postherpetic neuralgia, a painful complication of herpes zoster, occurs in 5% to 20% of those with herpes zoster (Mallick-Searle et al., 2016). In the UK, 19.5% and 13.7% of herpes zoster patients develop postherpetic neuralgia at least one and three months after diagnosis, respectively (Gauthier et al., 2008). Generally, it is estimated that neuropathic pain affects between 7% and 10% of the overall population (Van Hecke et al., 2014).

Numerous studies, including randomised controlled trials (RCTs) and meta-analyses (MAs), have confirmed the efficacy and safety of PGB and GBP in treating neuropathic pain (NP) conditions like painful diabetic peripheral neuropathy (pDPN) and neuralgia. The detailed findings from these studies are summarised in Table 1-1, highlighting the gabapentinoids' efficacy and tolerability in managing neuropathic pain.

Moore et al. (2018) demonstrated that GBP at a daily dosage of 1200mg significantly reduced PHN pain compared to a placebo, with a 50% improvement in pain for a third of patients and 30% for nearly half, questioning its effectiveness for others. Wiffen et al. (2017) noted increased effectiveness at higher doses ranging from 1800mg to 3600mg. Additionally, Zhang et al. (2018) associated GBP with improved sleep quality in PHN patients, though their findings may not reflect individual experiences due to the

reliance on mean differences. While GBP is effective for PHN, it's important to note the associated adverse events. Moore et al. (2018) and Wiffen et al. (2017) found higher withdrawal rates and more serious adverse events with GBP compared to placebo. Additionally, Zhang et al. (2018) reported increased peripheral oedema, dizziness, and sleepiness in GBP patients (Table 1-1).

Many studies have highlighted PGB as a treatment for PHN pain, yet a detailed examination of these studies is crucial for a deeper understanding. Parsons et al. (2018) observed significant pain relief with PGB doses ranging from 150mg to 600mg, though the variability in efficacy across this range was not detailed. Moreover, the statistical significance of these findings does not always imply clinical significance, which brings into question their real-world relevance. Derry et al. (2019) noted that higher doses of PGB provided more substantial pain relief, with a 300mg/d dose reducing pain by 30% to 50%, and even greater reductions at 600mg/d. However, these higher doses also led to more side effects, highlighting the need to balance efficacy with safety (Table 1-1). Additionally, Achar et al. (2013) found PGB more effective than AMT initially, but its efficacy waned by six months. This range of findings demonstrates the complexity of evaluating PGB's effectiveness and safety, underscoring the need for in-depth, long-term studies to thoroughly assess its benefits and risks in managing PHN (Table 1-1).

Moore et al. (2018) and Wiffen (2017) have indicated that GBP at doses of 1200 mg/d or higher effectively reduces pDPN pain and is generally well-tolerated, although patient responses vary. Despite confirming GBP's safety and efficacy over 12 weeks, Sekar et al. (2017) observed no significant improvement in sleep interference, questioning GBP's broader impact on patient well-being. Mahmood et al. (2011) found GBP more effective than carbamazepine in both pain relief and sleep quality

enhancement over a similar period, which highlights GBP's diverse therapeutic profile (Table 1-1). However, the specific design and comparator used may limit the generalisability of these findings. Moreover, higher dropout rates due to adverse events in studies by Wiffen et al. (2017) and Moore et al. (2018) suggest potential tolerability issues with GBP (Table 1-1).

Research by Derry (2019) consistently shows that gabapentinoids, such as PGB, at doses of 300-600 mg daily, effectively reduce pDPN pain compared to placebo. Comparative studies by Shahid et al. (2019) found no significant differences in pain reduction between DLX and PGB, although DLX showed a slight, non-significant edge by week 12. According to Enomoto et al. (2018) and Shahid et al. (2019), both drugs similarly improved quality of life. However, Tesfaye et al. (2013) noted that while combination therapy with DLX and PGB was effective, it did not significantly outperform high-dose monotherapy. These results suggest that DLX and PGB are effective on their own for improving pain and quality of life but combining them does not necessarily enhance outcomes compared to high doses of either drug alone. Additionally, patients in the PGB group experienced more adverse events (AEs) compared to placebo, as well as higher rates of serious AEs and discontinuations than those on DLX (Derry et al., 2019; Enomoto et al. 2018). Shahid et al. (2019) also observed a higher discontinuation rate due to AEs in the PGB group compared to DLX. Importantly, Tesfaye et al. (2013) found no significant difference in treatment-emergent adverse events between combination therapy and high-dose monotherapy (Table 1-1).

Research on the effectiveness of gabapentinoids for various neuropathic pain (NP) conditions such as mixed NP, spinal cord injury, post-traumatic pain, central pain, and HIV neuropathy are limited and shows mixed results. PGB was more effective than

placebo in reducing pain and sleep disturbances but did not significantly affect anxiety or depression, questioning its overall effectiveness in NP management (Onakpoya et al., 2019). Mixed findings on PGB's impact on QOL also suggest inconsistent benefits (Onakpoya et al., 2019) (Table 1-1). While PGB at 600 mg/d significantly reduced pain in post-traumatic and central neuropathic pain, it was ineffective for HIV neuropathy (Derry et al., 2019). Contradictory results from Markman et al. (2018) who reported that PGB did not significantly affect pain levels in post-traumatic neuropathic pain over 15 weeks, questioning the drug's claimed effectiveness. Additionally, a parallel-group RCT showed no significant differences in pain reduction between PGB, AMT, or their combination, complicating the narrative of PGB's effectiveness (Chakrabarty et al., 2019). Moreover, the lack of difference between gabapentin and placebo in some studies casts further doubt on its therapeutic utility (Moore et al., 2018) (Table 1-1).

Onakpoya et al. (2019) noted increased adverse events and higher discontinuation rates with PGB, raising safety concerns. In contrast, Markman et al. (2018) viewed PGB as highly tolerable, suggesting a possibly superior safety profile compared to other treatments. Chakrabarty et al. (2019) reported sedation as a common adverse event in studies comparing PGB, AMT, and their combination. Despite noting better efficacy and tolerance of combination therapy at higher doses, concerns remain about the overall safety and side effects (Chakrabarty et al., 2019) (Table 1-1). These conflicting reports underline the need for further research to clarify PGB's risk-benefit balance.

1.3.3.2 The efficacy and tolerability of gabapentin and pregabalin utilisation for the management of fibromyalgia

Fibromyalgia is a long-term disorder marked by extensive pain throughout the muscles and skeletal system (Clauw, 2014). It is often accompanied by symptoms such as

fatigue, disturbances in sleep, memory issues, and mood fluctuations (Clauw, 2014). Unlike neuropathic pain, which is caused by nerve damage the pain in fibromyalgia is believed to stems from atypical pain processing in the central nervous system (Clauw, 2014). Individuals with fibromyalgia frequently display increased pain sensitivity, intensely reacting to stimuli that would not usually cause pain – a phenomenon known as allodynia – and experiencing a heightened pain response to stimuli that are normally painful, known as hyperalgesia (Clauw et al., 2011). While the exact cause of fibromyalgia remains unidentified (Schmidt-Wilcke and Clauw, 2011), it is believed to be influenced by a combination of hereditary factors, environmental conditions, and psychological factors (Buskila and Sarzi-Puttini, 2006).

Fibromyalgia affects a significant portion of the population, though prevalence estimates can vary. It is estimated to affect approximately 3-8% of the population in Europe and South America, with higher prevalence in older age groups and in women than in men (Vincent et al., 2013; Jones et al., 2015). The prevalence in the United States is reported at 6.4%, with higher rates in women (7.7%) compared to men (4.9%) (Vincent et al., 2013). In the UK, research that applied the revised American College of Rheumatology (ACR) 2010 preliminary criteria for diagnosing fibromyalgia, which focuses on self-reported pain and physical symptoms, found that 5.4% of the population (N= 1,604) suffer from fibromyalgia (Jones et al., 2015).

Multiple MAs and RCTs have investigated the potential efficacy of gabapentinoids in alleviating pain among individuals diagnosed with FM. This review examined four MAs, two of which focused on PGB and two on GBP (Arnold, 2018; Cooper, 2017; Farag, 2022; Hauser et al., 2009). While GBP has not been as extensively studied as PGB, it could potentially serve as a substitute for PGB. Table 1-1 summarise the

characteristics of the included studies and the safety outcomes related to the use of gabapentinoids for FM pain management.

Cooper et al. (2017) reported a modest 30% reduction in fibromyalgia pain with GBP compared to placebo, but the study's reliance on low-quality data leaves the effectiveness of GBP uncertain. North et al. (2015), in an open-label trial, noted that increasing GBP to 1,800 mg/day reduced pain and improved daily functioning and sleep quality in FM patients, as per the fibromyalgia impact questionnaire (FIQ) (Table 1-1). However, the open-label design may bias these results, potentially overstating GBP’s benefits. Additionally, Hauser et al. (2009) conducted a meta-analysis focusing on PGB and GBP's efficacy and tolerability in FM, but included only one study on GBP, which showed significant pain relief and improved sleep but minimal impact on depression symptoms (Table 1-1). The scarcity of studies in this review, particularly for GBP, raises concerns about the generalisability of the findings and highlights the need for more extensive research to firmly establish GBP's effectiveness in treating FM symptoms, including mood disorders.

While gabapentin has shown effectiveness in managing FM pain and improving sleep, its safety profile raises concerns. Cooper et al. (2017) found a higher withdrawal rate due to AEs in the gabapentin group compared to placebo. Similarly, Hauser et al. (2009) reported more withdrawals due to AEs with GBP, highlighting issues like dizziness and weight gain (Table 1-1). These findings suggest that although gabapentin may benefit FM patients in pain management, its safety profile, particularly regarding the frequency and severity of AEs, warrants further comprehensive investigation to ensure patient safety.

Arnold et al. (2018) found that 300–450 mg/d of PGB reduced pain by 50% and sleep disturbances by 30% compared to placebo but emphasised the need for larger trials with active comparators to confirm efficacy. Farag et al. (2022) reported DLX 120mg/d as the most effective for pain relief, followed by PGB 450mg/d. They found that DLX, PGB, AMT, and milnacipran (except 200mg) improved sleep, with AMT and PGB 600mg being the most effective. Additionally, while all treatments except AMT aided in depression management, AMT was noted as the most tolerable (Table 1-1). This warrants further study due to potential oversimplifications of FM's impact on mental health. Acet et al. (2017) showed that both AMT and PGB significantly eased FM symptoms like sleep disruption and depression over three months, with AMT better for tender-point thresholds and PGB for neuropathic pain, underscoring the need for personalised treatment. Bidari et al. (2019) indicated DLX was more effective than PGB in a short four-week trial, raising questions about long-term effects. Zhang et al. (2021) also highlighted PGB's benefits in alleviating pain and improving sleep, suggesting these outcomes be considered alongside broader FM treatment impacts on mental health and quality of life (Table 1-1).

While PGB effectively reduces FM pain, Arnold et al. (2018) noted a concerning higher rate of treatment discontinuation due to AEs compared to placebo, highlighting a trade-off between efficacy and tolerability. Conversely, Bidari et al. (2019) found that DLX, despite its effectiveness, had a higher dropout rate and more frequent nausea than PGB, posing its own adherence and side effect challenges. Common AEs for PGB, such as drowsiness, dizziness, and somnolence (Hauser et al., 2009; Arnold et al., 2018; Zhang et al., 2021), emphasise the need for a careful balance between therapeutic benefits and daily life impacts. These findings underline the complexity of

managing FM with gabapentinoids, requiring careful consideration of potential pain relief against adverse effects and discontinuation risks (Table 1-1).

1.3.3.3 The efficacy and tolerability of gabapentin and pregabalin utilisation for the management of headache and migraine

Headaches, a prevalent neurological disorder, manifest as pain in the head, scalp, or neck region (Bigley, 2023). They come in various types, including tension-type, cluster, and sinus headaches (Ravisankar et al., 2015). The most frequently occurring type of headache is tension-type headache, which is typically characterised by a persistent pain or a sensation of pressure in the head, particularly in the temple region or at the back of the head and neck (Ravisankar et al., 2015). Migraines, a more intense category of headache, are usually identified by a throbbing or pulsing pain, commonly on one side of the head (Ravisankar et al., 2015). Accompanying symptoms of migraines often include light and sound sensitivity, nausea, and visual anomalies, known as auras (Andreou and Edvinsson, 2019).

Worldwide, active headache disorders are present in 52% of the population, with a higher incidence amongst females (57.8%) compared to males (44.4%) (Stovner et al., 2022). Tension-type headaches are approximately prevalent in 40% of the worldwide population, whilst migraines affect roughly 10%. Migraines are most commonly found in individuals between the ages of 25 and 55 years and are three times more frequent in females (Robbins and Lipton, 2010; Stovner et al., 2007). Migraines rank as the third most common and the second leading cause of disability across the globe, thus having a substantial impact (Feigin et al., 2019). The estimated global prevalence of migraines is around 14–15%, accounting for 4.9% of global health issues when quantified in years lived with disability (Steiner and Stovner, 2023). In the

UK, approximately 23% of people aged 15 to 69 years are estimated to suffer from migraines (Steel et al., 2018).

Numerous studies have assessed the efficacy of gabapentinoids in alleviating migraines and headaches, with mixed results. While evidence on GBP shows some potential in treating migraines, the effectiveness of PGB has been explored in several trials (Table 1-1 summarised the studies assessing the efficacy and safety of gabapentinoids in managing migraine and headache pain).

Leandri et al. (2001) found that GBP effectively treated resistant cluster headaches, achieving pain elimination within 8 days. However, its applicability to broader migraine treatments remains uncertain. However, Linde et al. (2013) highlighted the lack of evidence for GBP (900mg–2400mg/d) as a migraine preventative, showing no significant difference from a placebo in reducing migraine frequency. This challenges previous positive outcome and emphasises the necessity for additional studies. Meanwhile, Zain et al. (2013) reported that both topiramate and GBP (300mg–1200mg/d) were effective in preventing migraines, with topiramate being more effective in the initial month at reducing frequency and severity, as well as shortening attack duration (Table 1-1). This comparative study underscores the complexities of migraine management. Although GBP has proven effective in alleviating pain for headache and migraine sufferers, Zain et al. (2013) reported common adverse effects such as somnolence, dizziness, and weight gain. Despite these side effects, GBP was better tolerated than topiramate, marking it as a viable prophylactic option for migraines (Table 1-1). However, careful consideration is needed when comparing it with topiramate due to differing side effect profiles and patient tolerances.

Studies by Calandre et al. (2010), Pizzolato et al. (2011), and Zhang et al. (2015) document reductions in headache frequency and severity, less need for rescue medication, and improvements in Headache Impact Test-6 (HIT-6) scores and migraine allodynia with PGB treatment. Notably, Zhang et al. also reported significant improvements in migraine disability scores, but these findings need scrutiny due to potential study limitations such as design and sample size (Table 1-1). While these results are promising, they emphasise the need for more rigorous research to verify PGB's effectiveness in a diverse patient population. Furthermore, common adverse reactions like dizziness and somnolence were noted by Calandre et al., underscoring the importance of a broader drug safety assessment. Zhang et al.'s findings of low side effect incidence suggest good tolerance, yet they do not fully address potential long-term effects or subtle adverse reactions. The absence of serious adverse events in Pizzolato et al.'s study does not conclusively prove safety (Table 1-1). Overall, while early findings are encouraging, they call for more detailed research to thoroughly evaluate PGB's safety and long-term impact on migraine prevention.

1.3.3.4 The efficacy and tolerability of gabapentin and pregabalin utilisation for the management of musculoskeletal joint pain

Joint pain, a subset of musculoskeletal pain, specifically involves discomfort, aches, and soreness in the body's joints, such as knees, hips, and shoulders. It can be caused by various conditions, including arthritis (like osteoarthritis and rheumatoid arthritis), bursitis, and gout (Schaible et al., 2009).

Data from the National Health Interview Survey (NHIS) for the period of 2019 to 2021 estimates that 53.2 million adults in the US, or 21.2%, were diagnosed with arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia. During this period, the NHIS also

reported the unadjusted prevalence of arthritis to be 24.2% amongst women and 17.9% amongst men in the US (Fallon et al., 2023). OA affects approximately 32.5 million US adults (Collins et al., 2022). In the UK, rates for Rheumatoid Arthritis (RA) in 2014 showed an incidence of 3.81 per 10,000 person-years and a prevalence of 0.67% (Abhishek et al., 2017). For OA in 2017, the standardised incidence was recorded at 6.8 per 1000 person-years and the prevalence at 10.7%, with women experiencing higher rates than men (Swain et al., 2020).

Despite using paracetamol, NSAIDs, and opioids, many OA and RA patients still suffer from chronic pain (NICE, 2014; Zhang et al., 2007). The ideal joint pain medication should offer long-lasting relief and minimal side effects. Gabapentinoids have become notable for their effectiveness in reducing pain sensitivity, which is crucial as arthritis involves both nociceptive and neuropathic pain (Pan et al., 2016; Patel and Dickenson, 2016). However, few studies have specifically examined gabapentinoids like GBP and PGB for arthritis pain management (refer to Table 1-1 reviewed studies evaluating the effectiveness and safety of gabapentinoids in the treatment of musculoskeletal joint pain).

The limited research on GBP and PGB for treating arthritis pain requires careful interpretation. A 2019 RCT by Enteshari-Moghaddam et al., which compared the efficacy of DLX, GBP, and acetaminophen (AC) in knee-related OA, found GBP and DLX similarly effective and tolerable for pain relief and functional status. The study showed lower pain Visual Analogue Scale (VAS) and Western Ontario and McMaster (WOMAC) scores for GBP and DLX compared to AC (Table 1-1). Yet, the lack of significant differences between GBP and DLX suggests that while beneficial, neither medication is clearly superior for OA pain. This underscores the need for more detailed research to determine their relative efficacy in managing arthritis pain.

Some studies support the effectiveness of NSAIDs and PGB in alleviating arthritis joint pain, but further evaluation is necessary. Ohtori et al. (2013) showed that combining PGB (25 mg) with meloxicam (10 mg) significantly lowered pain scores compared to using either drug alone. However, the superiority of this combination needs verification in larger, diverse patient groups. Sofat et al. (2017) found PGB more effective than DLX, with significant improvements over placebo, highlighting PGB's potential but also the need to consider individual responses and patient factors. Additionally, Filatova et al. (2019) indicated that PGB combined with Disease-Modifying AntiRheumatic Drugs (DMARDs) improved pain intensity in RA patients more than DMARDs alone, suggesting the advantages of multimodal treatment strategies (Table 1-1).

However, a critical gap in these studies is the absence of information on AEs or withdrawals due to AEs, essential for fully understanding drug safety and tolerability. This lack of data highlights the need for more comprehensive research that addresses both the efficacy and safety of treatments for arthritis joint pain.

1.3.3.5 The efficacy and tolerability of gabapentin and pregabalin utilisation for the management of back pain

Back pain is a common issue that impacts the lower, middle, or upper regions of the back. Its severity can vary, manifesting as either a persistent, mild ache or an abrupt, intense pain. Its origins are diverse, ranging from strained muscles or ligaments to issues with intervertebral discs, arthritis, or abnormalities in the skeletal structure (NIH, 2023). Low back pain, the most common type of back pain, is recognised as a global health issue, causing significant personal, social, and economic challenges (Hoy et al., 2012).

Globally, in 2017, the age-standardised point prevalence rate of lower back pain (LBP) was 7.50%. During this time, it was estimated that approximately 577.0 million people were suffering from LBP at any given moment. Additionally, the prevalence rates of LBP were observed to be higher in females than in males (Wu et al., 2020).

The current evidence regarding gabapentinoids for back pain is limited, highlights the potential for AEs, and shows restricted efficacy (Table 1-1: summarised the literature concerning the efficacy and safety of gabapentinoids in the treatment of back pain).

Gewandter (2019) found that an extended-release GBP was ineffective in significantly reducing pain in patients with persistent back pain or post-surgery (Table 1-1). This finding aligns with a meta-analysis by Enke et al. (2018), which showed that GBP and PGB do not effectively alleviate pain or disability in the short term for low back or lumbar radicular pain compared to placebo. Furthermore, Migliorini et al. (2020) found that treatments like baclofen, DLX, NSAIDs, and opiates are more effective for chronic lower back pain than gabapentinoids. Kolber et al. (2021) also reported that gabapentinoids were not effective in reducing pain in patients with LBP, noting that exercise, oral NSAIDs, and DLX provided greater, more lasting benefits (Table 1-1). These findings suggest a need to reconsider the role of gabapentinoids in back pain management due to their limited effectiveness and the availability of better options.

Enke et al. (2018) found a higher incidence of AEs with gabapentinoids compared to placebo, a finding supported by Kolber et al. (2021), who noted more frequent AEs in the GBP group. Additionally, Gewandter et al. (2019) reported common symptoms like dizziness and somnolence amongst GBP users (Table 1-1). These findings raise concerns about the safety profile of gabapentinoids, especially given their extensive use in pain management. The increased risk of AEs, particularly those impairing daily

functions such as dizziness and somnolence, underscores the need for cautious prescribing and prioritising patient well-being in pain management strategies.

Table 1-1: Summary of Studies on the Efficacy and Tolerability of Pregabalin and Gabapentin for Diverse Pain Conditions

Author, Year, Country	Study Design	NP condition	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Neuropathic pain									
Mahmood et al. 2011 Pakistan	Open label	DNP	60	GBP vs CBZ	200-900 mg/d vs 400-1200 mg/d	12	**Pain scale** **GBP:** VAS was 6.17±0.15 to 3.5±0.15; 43.3% from baseline; p=0.001 **CBZ:** 6.07±0.13 to 4.23±0.13; 30.4% from baseline; p=0.001.	GBP	Not measured
Achar et al. 2013 India	open ended	PHN	50	PGB vs AMT	75mg BID vs 25mg/d	24	**Improvements in pain perception** PGB vs AMT **At the end of 8 weeks:** 36%vs 8%, p<0.05 **At the end of 16 weeks:** 61.9%vs 27.8%, p<0.05 **At the end of 24 weeks:** 52.38% vs 36.84%, p>0.05	PGB	**Patients with AEs** PGB vs AMT OR = 1.64 95% CI [0.46–5.97]
Tesfaye et al. 2013 Europe	Multicentre, double-blind, parallel-group study	DNP	1,143	DLX vs PGB then DLX or PGB vs DLX+PGB	60mg/d vs 300mg/d then 120mg or 600mg vs 60mg +300mg	Initial therapy= 8 weeks Then Second phase = 8 weeks	**BPI-MSF average pain** **Initial therapy** DLX vs PGB **At 4 weeks** MMRM: -1.76 vs -1.40; MD: -0.37 (-0.63, -0.10) P = 0.007 **At 8 weeks** MMRM: -2.30 vs -1.68; MD: -0.61(-0.90, -0.33) P < 0.001 **Second phase** Combination vs high-dose monotherapy MMRM: -2.35 vs -2.16; MD: -0.19;(-0.61, -0.23) P = 0.370 **≥50% reduction in BPI-MS 24-hour average pain** **Initial therapy** DLX vs PGB 40.3% vs 27.8%; P<0.001	Not significant No difference	**Patients with AEs** **Initial therapy** DLX vs PGB 55.6% vs 57.6% **Combination/ high-dose monotherapy** DLX+PGB vs high dose DLX 36.7% vs 27.4% DLX+PGB vs high dose PGB 36.7% vs 38.1% **Patients with SAEs** **Initial therapy** DLX vs PGB 3% vs 3.2% **Combination/ high-dose monotherapy** DLX+PGB vs high dose DLX 4.7% vs 4.1

Author, Year, Country	Study Design	NP condition	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Neuropathic pain									
Tesfaye et al. 2013 Europe Cont.							Combination vs high-dose monotherapy 52.1% vs 39.3%; P = 0.068		DLX+PGB vs high dose PGB 4.7% vs 2.1% **Discontinuation due to AEs** **Initial therapy** DLX vs PGB 11.5% vs 12.4% **Combination/ high-dose monotherapy** DLX+PGB vs high dose DLX 4.1% vs 6.8% DLX+PGB vs high dose PGB 4.1% vs 3.1%
Wiffen et al. 2017 UK, Norway, Germany	Meta-Analysis	Chronic NP from PHN or PDN	5914	GBP vs placebo	1200-3600mg/d	4-12	**PHN** GBP vs Placebo **Substantial benefit*:** 32% vs 17%, RR 1.8 (1.5 to 2.1), NNT 6.7 (5.4 to 8.7) **Moderate benefit*:** 46% vs 25%, RR 1.8 (1.6 to 2.0) , NNT 4.8 (4.1 to 6.0) **PND** GBP vs Placebo **Substantial benefit:** 38% vs 21%, RR 1.9 (1.5 to 2.3), NNT 5.9 (4.6 to 8.3) **Moderate benefit:** 52% vs 37% , RR 1.4 (1.3 to 1.6), NNT 6.6 (4.9 to 9.9)	GBP	**Patients with AEs** GBP vs Placebo 63% vs 49% **Patients with SAEs** GBP vs Placebo 3.2% vs 2.8% **Discontinuation due to AEs** GBP vs Placebo 11% vs 8.2%
Sekar et al. 2017 India	Open Label Parallel Group	DNP	100	GBP vs AMT	600 up to 1800 mg/d vs 25 up to 75mg/d	12	**Mean VAS** bassline vs third visit (12 weeks) **GBP:** 67.72±16.93 vs 29.51±16.90; percentage change= -56.42%, p<0.0001. **AMT:** 65.92±12.89 vs 36.85±14.14 percentage change= -44.10%, p<0.0001.	GBP	Not measured

Author, Year, Country	Study Design	NP condition	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Neuropathic pain									
Sekar et al. 2017 India Cont.							**Mean VAS at final visit 12 week** GBP vs AMT 29.51±16.90 vs 36.85±14.14; P= 0.024 **Mean daily SIS from VAS** bassline vs third visit (12 weeks) GBP vs AMT 6.72±1.91vs 5.96±2.09 to 3.73±1.78 vs 4.46±2.23; p=0.079		
Moore et al. 2018 Canada, UK, US, China, Germany , India, Italy, Mexico, Sweden	Meta-Analysis	Chronic NP from PHN or PDN	5914	GBP vs placebo	1200-3600mg/d	4-12	**PHN** GBP vs Placebo **Substantial benefit:** 32% vs 17% **Moderate benefit:** 46% vs 25% **PND** GBP vs Placebo **Substantial benefit:** 38% vs 21% **Moderate benefit:** 52% vs 37% **Other NP :** No difference between gabapentin and placebo	GBP	**Patients with AEs** GBP vs Placebo 63% vs 49% **Patients with SAEs** GBP vs Placebo 3% vs 3% **Discontinuation due to AEs** 11% vs 8%
Zhang et al. 2018 US, UK, China, France	Meta-analysis	PHN	2376	GBP (ER or GEn) vs placebo	**GBP ER** 1800 mg/d **GBP GEn** 1200, 2400, 3600 mg/d	-	**Change in ADP score** **REM:** MD=−0.91, (95%CI −1.32 to −0.51), P<0.00001 **FEM:** MD=–0.75, (−0.77 to −0.73), P<0.00001 **Substantial benefit** **REM:**RR=1.79, (1.43 to 2.25), P<0.00001 **FEM:**RR=1.75, (1.50 to 2.05), P<0.00001 **Sleep Rating Scores** **REM:** SMD=−0.44, (−0.66 to −0.23), P<0.0001 **FEM:** SMD=−0.39, (−0.52 to −0.27), P<0.00001	GBP	**Patients with AEs** GBP vs Placebo REM: RR = 1.29, P= 0.010 FEM: RR=1.34, P= <0.00001
Enomoto et al. 2018 Japan	Double blind, non-inferiority comparative study	DNP	303	DLX vs PGB	40–60 mg/d vs 300 – 600 mg/d	12	**The 24-hour NRS average PS** DLX vs PGB LS mean (SE): –2.286 (0.133) vs –2.358 (0.133). The treatment difference (CI): 0.072 (–0.295, 0.439)	Not significant No difference	**Patients with AEs** DLX vs PGB 29.6% vs 35.8% **Patients with SAEs** DLX vs PGB 0.7% vs 4%

Author, Year, Country	Study Design	NP condition	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Neuropathic pain									
Enomoto et al. 2018 Japan Cont.									**Discontinuation due to AEs** DLX vs PGB 6.6%¥ vs 7.9%¥
Markman et al. 2018 USA	Double-blind, placebo-controlled	PTNP	539	PGB vs placebo	Flexibly dosed 150–600 mg/d	15	PGB vs placebo **Mean change of PS** − 0.22 (CI) (− 0.54, 0.10); P= 0.182 **Sleep interference** LS MD (SE) [CI]: − 0.43 (0.15) [− 0.71, − 0.14], P= 0.003	Not significant No difference	**Patients with AEs** PGB vs Placebo 50.4% vs 40% **Discontinuation due to AEs** PGB vs Placebo 19.3% vs 6%
Parsons et al. 2018 China and international	Double-blind, placebo-controlled	PHN	1166 (Chinese = 312 Inter. = 854)	PGB vs placebo	Fixed dose (150, 300, 600 mg/d) or flexible (150–600 mg/d)	8	PGB vs placebo **MPS** **Chinese vs international** LSMD [CIs]: –0.8 [–1.2, –0.5] vs –1.3 [–1.6, –1.0]; p<0.001.	PGB	Not measured
Chakrabarty et al. 2019 India	Parallel-group, open-label interventional study	NP	147	PGB vs AMT vs combo (PGB+ AMT)	150 mg vs 25mg vs (75mg +10mg)	12	**After 4, 8, and 12 weeks** There was no significant difference in the mean NPSI score between the groups (P > 0.05). **At week 12** PGB vs AMT vs Combination 24.129±6.125 vs 23.452±8.801 vs 21.133±6.977; P =0.0911	Not significant No difference	**Patients with AEs** PGB vs AMT vs Combo Sedation 10.9% vs 14.1% vs 16.3% Dizziness 2.2% vs 6.5% vs 3.3% Vertigo 8.7% vs 6.5% vs 6.5%
Derry et al. 2019 UK, Norway, Canada	Meta-analysis	Chronic NP from PHN, PDN, mixed NP, PTNP, CNP, HIV NP	11,906	Pregabalin vs placebo	150-300-600 mg/d	2-16	**PHN** PGB 300mg **Substantial benefit:** 32% vs 13%, RR 2.5 (1.9 to 3.4), NNT 5.3 (3.9 to 8.1) **Moderate benefit:** 50% vs 25%, RR 2.1 (1.6 to 2.6), NNT 3.9 (3.0 to 5.6) PGB 600mg **Substantial benefit:** 41% vs 15%, RR 2.7 (2.0 to 3.5), NNT 3.9 (3.1 to 5.5)	PGB	**Patients with AEs** PGB(300mg) vs Placebo **PHN** Somnolence 16% vs 5.5% Dizziness 29% vs 8.1%

Author, Year, Country	Study Design	NP condition	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Neuropathic pain									
Derry et al. 2019 UK, Norway, Canada Cont.							**Moderate benefit:** 62% vs 24%, RR 2.5 (2.0 to 3.2), NNT 2.7 (2.2 to 3.7) **PND** PGB 300mg **Substantial benefit:** 31% vs 24%; RR 1.3 (95% CI 1.2 to 1.5); NNT 22 (12 to 200) **Moderate benefit:** 47% vs 42%, RR 1.1 (1.01 to 1.2); NNT 22 (12 to 200) PGB 600mg **Substantial benefit:** 63% vs 52%; RR 1.2 (1.04 to 1.4); NNT 9.6 (5.5 to 41) **Moderate benefit:** 41% vs 28%; RR 1.4 (1.2 to 1.7); NNT 7.8 (5.4 to 14)		**PDN** Somnolence 11% vs 3.1% Dizziness 13% vs 3.8% PGB(600mg) vs Placebo **PHN** Somnolence 25% vs 5.8% Dizziness 35% vs 8.8% **PDN** Somnolence 15% vs 4.5%Dizziness 22% vs 4.4%
Onakpoya et al. 2019 US, China, Denmark, Sweden, South Africa, Czech Republic, India, Asia, Slovenia, Australia, Korea, Japan, UK, Spain	Meta-analysis	NP	6087	PGB vs placebo	150, 300, 600mg/d	3-20	**Pain:** SMD: −0.49 (−0.66 to −0.32, p<0.00001). **Sleep interference scores:** SMD −0.38 (−0.50 to −0.26, p<0.00001 **Quality of life:** pregabalin's effectiveness shows inconsistency, with half the studies indicating significant benefits over placebo, while the other half report no notable advantage. **Anxiety:** p=0.14 **Depression:** p=0.54	PGB	**Patients with AEs** PGB vs placebo RR = 1.33, P = <0.00001 **Patients with SAEs** PGB vs placebo RR = 0.9, P = 0.50 **Discontinuation due to AEs** PGB vs placebo RR = 1.91, P = <0.00001
Shahid et al. 2019 Pakistan	Open label	DNP	161	DLX vs PGB	60 mg/d vs 300 mg /day	12	**Mean VAS score** Baseline to 12 weeks **DLX:** 6.81 ± 0.91 to 4.01 ± 1.12; p<0.0001 **PGB:** 6.99 ± 1.12 to 4.91 ± 0.82; p<0.0001 **Mean change in VAS score** DLX vs PGB - 2.80 vs - 2.08; P=0.90	Not significant No difference	**Patients with AEs** PGB vs DLX 8.1% vs 1.1% **Discontinuation due to AEs** PGB vs DLX 2.3% vs 0%

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Fibromyalgia pain								
Hauser et al. 2009 Germany	Meta-analysis	3,478	GBP or PGB vs placebo	GBP 1,200mg–2,400mg/d PGB 450mg, 300mg or 600 mg/d	11	**Reduction of pain (PGB and GBP):** SMD (95%CI) - 0.28, (- 0.36, - 0.20) **Improve in sleep (PGB and GBP) :** SMD (95%CI) - 0.39, (- 0.48, - 0.39) **Improved in HRQOL (PGB):** SMD (95%CI) - 0.30, (- 0.46, - 0.15) **Depression (PGB and GBP):** SMD (95%CI) - 0.12 (- 0.30, 0.06) **Fatigue (PGB):** SMD (95%CI) - 0.16, (- 0.23, - 0.09) **Anxiety (PGB):** SMD (95%CI) - 0.18, (-0.27, - 0.10) With a P < 0.001 for all outcomes except depression (p=0.18).	GBP and PGB	**Patients with AEs** Placebo Dizziness: 10% Somnolence: 5% Fatigue: 4% Peripheral oedema: 2% GBP 1200mg–2400mg Dizziness: 25% Somnolence: 19% Fatigue: 8% Peripheral oedema: 16% PGB 150mg Dizziness: 23% Somnolence: 16% Fatigue: 5% Peripheral oedema: 5% PGB 300mg Dizziness: 32% Somnolence: 20% Fatigue: 7% Peripheral oedema: 6% PGB 450mg Dizziness: 42% Somnolence: 21% Fatigue: 8% Peripheral oedema: 6% PGB 600mg Dizziness: 46% Somnolence: 23% Fatigue: 6% Peripheral oedema: 8% **Patients with SAEs** Placebo: 3% PGB 300mg: 10% PGB 450mg: 9% PGB 600mg: 12%

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Fibromyalgia pain								
Hauser et al. 2009 Germany Cont.								**Discontinuation Due to AEs** Placebo: 9% GBP 1200mg–2400mg: 16% PGB 150mg: 8% PGB 300mg: 17% PGB 450mg: 20% PGB 600mg: 27%
North et al. 2015 USA	Open-label, single-arm	29	GBP ER	1800mg/d	12	**Pain** Weeks 4, 8, and 12 vs baseline MD: -2.52, -3.19, and -3.33, P<0.0001 **FIQ scores** Weeks 4, 8, and 12 vs baseline MD: -28.30, -29.9, and -31.2, P<0.0001 **Sleep disturbance** Weeks 4, 8, and 12 vs baseline P<0.0001 **Sleep duration** Week 12 vs baseline P = 0.0165	GBP	**Patients with AEs** GBP ER 1800 mg/d Drowsiness: 27.5% Dizziness and irritability: 10% Weight gain: 6.8% **Patients with SAEs** GBP ER 1800 mg/d 6.8%
Cooper et al. 2017 UK	Meta-analysis	150	GBP vs placebo	1200mg and 2400 mg/d	12	**Pain intensity** GBP vs Placebo **Moderate benefit*:** 49% vs 39%	GBP	**Discontinuation Due to AEs** GBP vs placebo 16% vs 9%
Acet et al. 2017 Turkey	RCT	Females only (71)	PGB vs AMT	450mg vs 25 mg	12	**Pain (VAS)** AMT vs PGB (pre-treatment) 7.42±1.67 vs 8.04±1.44 AMT vs PGB (post-treatment) 4.26±1.93 vs 4.27±1.83 P>0.05 **FIQ-pain** AMT vs PGB (pre-treatment) 7.72±1.71 vs 7.91±1.65 AMT vs PGB (post-treatment) 3.56±1.82 vs 4.50±1.80 P=0.04	Both drugs	**Patients with AEs** **Dizziness** PGB vs AMT 6.2% vs 2.3%

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Fibromyalgia pain								
Acet et al. 2017 Turkey Cont.						**Tender point score** AMT vs PGB -0.197±0.14 vs -0.098±0.12, P= 0.005 **Myalgic score** AMT vs PGB -0.160±0.13 vs -0.079±0.11, P= 0.012 **LANSS** P<0.05, a greater degree of improvement was seen in the PGB group compared with the AMT group		
Arnold et al. 2018 Global	Systematic review	5,217	PGB vs placebo	75mg–600mg/d	3–32	The quality of sleep, the severity of pain, and the status of the patient improve significantly.	PGB	**Patients with AEs** PGB vs placebo 77.3%-91.8% vs 59.9%-77.1%. **Patients with SAEs** PGB vs placebo 0.6%–4.4% vs 0.4%–2.2% **Discontinuation Due to AEs** PGB vs placebo 6.1%–22.4% vs 3.4%–10.9%
Bidari et al. 2019 -	Open label randomised trial	99	DLX vs PGB	30-60 mg vs 75-150 mg	4	**WPI score** MD in score change − 2.32, 95% CI, −4.46 to − 0.18; p = 0.034	DLX	Not measured
Zhang et al. 2021 China	Double blind phase III local registration trial	334	PGB vs placebo	300-450 mg/d	14	**Pain** LSMD [95% CI]: –0.73 [–1.10 to –0.36]; P=0.0001 **Improvement in sleep** LSMD= 9.03; P=0.0003	PGB	**Patients with AEs** PGB vs placebo 70% vs 62.8% **Patients with SAEs** PGB vs placebo 0% vs 5.5% **Discontinuation Due to AEs** PGB vs placebo 12.9% vs 6.7%

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Fibromyalgia pain								
Farag et al. 2022 USA, UK	Meta-analysis	11,930	AMT, PGB, DLX, and Milnacipran vs placebo	AMT (off label) PGB (150mg, 300mg, 450mg or 600 mg/d) DLX (60mg–120mg/d) Milnacipran (100mg–200mg/d)	4–27	**Pain** DLX (120 mg/d) vs placebo: SMD: −0.33; 95% CI, −0.36 to −0.30 PGB (450 mg/d) vs placebo: SMD, −0.30; 95% CI,−0.32 to −0.27 Milnacipran vs placebo: SMD,−0.17; 95% CI, −0.20 to −0.15 **Reduced sleep disturbances** AMT vs placebo: SMD: −0.97; 95% CI, −1.10 to −0.83 PGB (600mg/d) vs placebo: SMD: −0.60; 95% CI,−0.67 to −0.54 DLX (60 mg/d) vs placebo: SMD, −0.21;95% CI, −0.30 to −0.13 **Fatigue** AMT vs placebo: SMD:−0.64; 95% CI, −0.75 to −0.53 PGB (150 mg/d) vs placebo: SMD: −0.27; 95% CI, −0.29 to −0.24 PGB (600 mg/d) vs placebo: SMD: −0.25; 95% CI, −0.36 to−0.14 Milnacipran (100 mg/d) vs placebo: SMD, −0.10; 95% CI, −0.14 to −0.05 DLX 120 mg/d vs placebo: SMD: −0.12; 95% CI, −0.16 to −0.08 **QOL** AMT vs placebo: SMD: −0.80; 95% CI,−0.94 to −0.65 DLX (120mg/d) vs placebo: SMD: −0.39; 95% CI, −0.55 to −0.23 DLX (60 mg/d) vs placebo: SMD: −0.22; 95% CI, −0.35 to−0.09 PGB (450 mg/d) vs placebo: SMD: −0.18; 95% CI, −0.29 to −0.06 PGB (300 mg/d) vs placebo: SMD: −0.14; 95% CI, −0.23 to −0.06 PGB (150 mg/d) vs placebo: SMD: −0.12; 95% CI, −0.23 to −0.02	DLX and PGB	Not measured

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Fibromyalgia pain								
Farag et al. 2022 USA, UK Cont.						**Depression** DLX (120mg/d) vs placebo: SMD: −0.25; 95% CI, −0.32 to −0.17 DLX(60mg/d) vs placebo: SMD: −0.24; 95% CI, −0.27 to −0.20 PGB (600mg/d)vs placebo: SMD: −0.23; 95% CI, −0.28to −0.17 PGB (300mg/d) vs placebo: SMD: −0.22; 95% CI, −0.26 to −0.19 PGB (450mg/d) vs placebo: SMD: −0.14; 95% CI, −0.18 to −0.09) PGB (150 mg/d) vs placebo: SMD: −0.04; 95% CI, −0.07 to −0.02 Milnacipran (100mg/d) vs placebo: SMD: −0.10; 95% CI, −0.12 to −0.07 Milnacipran (200 mg/d) vs placebo: SMD: −0.07; 95% CI, −0.10 to −0.04)		
Migraine and headache pain								
Leandri et al. 2001 Italy	Open-pilot study	12	GBP	300mg TID	1	All patients experienced pain relief after just eight days of beginning therapy, with bout durations decreased to 16±40% of their previous bout average.	GBP	Not measured
Calandre et al. 2010 Spain	Open-label study	30	PGB	125mg–450mg/d	12	**Frequency of headaches, intake of rescue medication** and **HIT-6 scores:** P < 0.0001 **Severity:** P = 0.0005	PGB	**Patients with AEs** Dizziness: 40% Somnolence: 29% Abnormal thinking:16.7%
Pizzolato et al. 2011 Italy	Independent, uncontrolled, open label, observational, prospective study	47	PGB	75mg–300mg/d	12	Compared to baseline **The frequency of migraine in 1 and 3 months,** (-32 and -31%,), P<0.001 **A 50% reduction in headache days per month:** 26% **Reduced attack frequency by at least ¼:** 60%	PGB	**Patients with AEs** 13% **Patients with SAEs** 0% **Discontinuation Due to AEs** 6.4%

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Migraine and headache pain								
Linde et al. 2013	Meta-analysis of RCT	1,009	GBP or PGB vs placebo	GBP = 900mg–2400mg/d	≥12	**Headache frequency** GBP vs placebo MD: -0.44; 95% CI -1.43 to 0.56	Not significant	Not measured
Zain et al. 2013 Pakistan	Open-label RCT	80	Topiramate vs GBP	Topiramate = 50mg–200mg/d vs GBP = 300mg–1200mg/d	12	**Mean monthly migraine frequency** Topiramate vs GBP (10.67±4.25 to 1.82±2.02) vs (11.97±4.452 to 2.73±2.59), P<0.001 **Severity** Topiramate vs GBP (6.60±2.122 to 1.03±0.92) vs (6.93±1.90 to 1.18±1.01), p<0.001 **Average duration of attacks** Topiramate vs GBP (25.77±22.32 to 1.05±1.06 hours) vs (22.20±20.72 to 1.08±1.40 hours), p<0.001	Topiramate	**Patients with AEs** Topiramate Weight loss: 22.5% Numbness: 5% GBP Dizziness: 7.5% Weight gain: 7.5% Somnolence: 5%
Zhang et al. 2015 China	Prospective cohort study	63	PGB	300mg–600mg/d	12	Compared with baseline **ASC scores** Decreased, p<0.05 **The frequency** 11.7 ± 6.3 vs 4.6 ± 1.8, p < 0.001 **Severity** 5.5 ± 2.1 vs 3.0 ± 2.7, p < 0.001 **Duration of headache** 13.3 ± 8.9 vs 8.1 ± 5.0, p < 0.01 **MIDAS** 83.3 ± 32.4 vs 41.8 ± 31.8, p < 0.001 **HIT-6 scores** 66.9 ± 6.9 vs 57.2 ± 5.5, p < 0.001	PGB	**Patients with AEs** Dizziness:7.3% Dry mouth: 4.9% Weight gain:1.4%

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Musculoskeletal joint pain								
Ohtori et al. 2013 Japan	Randomised prospective study	89	Meloxicam vs PGB vs PGB + Meloxicam	Meloxicam 10mg vs PGB 25mg vs 10mg + 25mg	4	**VAS Pain** **Compared to combination** Baseline vs after treatment (4 wks) **Meloxicam** 5.6±2.1 vs 2.0±2.1, P=0.02 **PGB** 5.0±2.0 vs 2.0±2.2, P=0.03 **Meloxicam + PGB** 5.4±2.2 vs 1.0±1.2 **WOMAC pain (4 wks)** Baseline vs after treatment (4 wks) **Meloxicam** 12.3±3.3 vs 6.3±2.3, P=0.043 **PGB** 12.2±3.0 vs 6.6±3.0, P=0.045 **Meloxicam + PGB** 12.0±3.7 vs 3.6±1.7	Combo PGB + meloxicam	Not measured
Sofat et al. 2017 UK	Randomised prospective study	65	DLX vs PGB vs placebo	DLX 30mg vs PGB 150mg	12	**NRS pain** PGB vs placebo MD (95% CI): –2.7 (–3.5 to –1.9), P=0.023 DLX vs placebo MD (CI) –2.3 (–3.8 to –0.9), P= 0.19 **AUSCAN pain** PGB vs placebo MD (CI) –132.1 (–181.1 to –82.9), P=0.008 DLX vs placebo MD (CI) –35.8 (–119.7 to 48.2), P= 0.59 **Use of rescue medication** PGB vs placebo :9 vs 56 days DLX vs placebo: 5 vs 56 days	PGB	Not measured

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Musculoskeletal joint pain								
Filatova et al. 2019 Russia	RCT	80	PGB + DMARDs vs DMARDs	-	5	**VAS pain intensity** Baseline vs after treatment PGB + DMARDs **At week 2** 77.0±13.5 vs 48.8 ± 14.2 **At week 5** 77.0±13.5 vs 48.3 ± 34.2 DMARDs **At week 2** 75.2±14.7 vs 72.9 ±16.9 **At week 5** 75.2±14.7 vs 64.5 ± 20.2 P= 0.004	Combo PGB + DMARD	Not measured
Enteshari-Moghaddam et al. 2019 Iran	RCT	150	DLX vs GBP vs AC	DLX 30mg vs GBP 300mg vs AC 1000mg	12	**VAS pain** DLX vs AC -61.45 ± 7.65 vs − 31.20 ± 12.58, p<0.001 GBP vs AC -63.36 ± 8.87 vs − 31.20 ± 12.58, p<0.001 **WOMA Pain subscale** DLX vs AC -78.29 ± 10.06 vs − 50.32 ± 10.78, p<0.001 GBP vs AC -73.94 ± 12.79 vs − 50.32 ± 10.78, p<0.001	DLX and GBP	Not measured

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Back pain								
Enke et al. 2018	SR of RCTs	859	GBP or PGB vs placebo	GBP 300mg–3600mg PGB 300mg–600mg	2–34	**Low back pain** **Pain using NPRS** GBP vs placebo MD=–0.0, 95% CI –0.8 to 0.7 **Disability using ODI** GBP vs placebo MD –0.2, 95% CI –5.9 to 5.5 **Lumbar radicular pain** **Pain using NPRS** GBP or PGB vs placebo MD –0.1, 95% CI –0.7 to 0.5 **Disability using RMQ** GBP or PGB vs placebo **Short-term** MD 0.6, 95% CI –1.5 to 2.7 **Intermediate term** MD –1.4, 95% CI –3.6 to 0.8 **Long-term** MD 0.8, 95% CI –1.5 to 3.1	No benefit	**Patients with AEs** GBP vs placebo More in GB RR = 1.4 (1.2 - 1.7) PGB vs placebo More in PGB RR= 0.9 (0.1–12.2)
Gewandter et al. 2019 USA	Double-blind crossover trial	32	ER GBP vs placebo	1800mg/d	16 with 10 days for wash-out period	**FBSS** **Mean 7-day NRS pain score** ER GBP vs placebo LSMD[CI]=-0.01 [-0.22 to 0.20]	No difference	**Patients with AEs** ER GBP vs placebo **Dizziness** 18% vs 13% **Somnolence** 32% vs 0%
Migliorini et al. 2020 Global	MA of RCTs	285	Acetaminophen, amoxicillin, flupirtine, baclofen, TCAs, duloxetine, topiramate, gabapentinoid, NSAIDs or opioids	-	1–56	**Pain using VAS** Gabapentinoids 46.78 ± 24.1 to 39.35 ± 15.3 (−7.43 points; P = 0.08) Baclofen 64.55 ± 0.1 to 50.95 ± 11.5 (−13.60 points; P = 0.05) DLX 58.00 ± 25.0 to 41.00 ± 29.0 (−17.00 points; P = 0.04).	Baclofen DLX NSAIDs Opiates	Not measured

Author, Year, Country	Study Design	Sample Size	Drugs	Dose (mg/d)	Duration (Weeks)	Results	Favour Drug for PD	Tolerability
Back pain								
Migliorini et al. 2020 Global Cont.						NSAID 60.27 ± 16.2 to 38.06 ± 6.2 (−22.20 points; P = 0.002) Opiates 67.32 ± 11.9 to 41.53 ± 10.5 (−24.99 points; P < 0.0001)		
Kolber et al. 2021 France	SR of RCTs	108	Injections of CS, paracetamol, opioids, NSAIDs, exercise, lumbar manipulation therapy, acupuncture anticonvulsants, TCAs, SNRIs, SSRI, cannabinoids, oral muscle relaxants or topical rubefacients	-	4–104	**Pain** Exercise RR=1.71; 95% CI 1.37 to 2.15; NNT=7 Oral NSAIDs RR = 1.44; 95% CI 1.17 to 1.78; NNT = 6 DLX RR= 1.25; 95% CI 1.13 to 1.38; NNT= 10 GBP vs placebo At week 12 : 22% vs 26%; p=0.6	Exercise NSAIDs SNRIs (DLX)	**Patients with AEs** GBP vs placebo **Dizziness** 43.6% vs 26.4% **Fatigue** 49% vs 28% **Sleep disturbances** 50.9% vs 39.6% **Discontinuation Due to AEs** GBP vs placebo 13% vs 9%

*Substantial benefit defined as ≥50% reduction in pain intensity; moderate benefit defined as ≥30% reduction in pain intensity.

¥ The difference was not statistically significant P≥0.05.

AC: acetaminophen; ADP: Average Daily Pain; AEs: adverse effects; AMT: amitriptyline; ASC: allodynia symptom checklist; AUSCAN: Australian and Canadian hand osteoarthritis index; BID: twice daily; CBZ: carbamazepine; CI: confidence interval; CNP: central neuropathic pain; d: daily; combo: combination; Cont.: continue; CS: corticosteroids; DLX: duloxetine; DMARDs: disease-modifying antirheumatic drugs; DNP: diabetic neuropathic pain; ER: extended release; FBSS: failed back surgery syndrome; FEM: fixed effect model: FIQ: fibromyalgia impact questionnaire; GBP: gabapentin; GEn: gabapentin enacarbil; HIT-6: headache impact test-6; HIV: human immunodeficiency virus; LANSS: Leeds assessment of neuropathic symptoms and signs; LSMD: lean square mean difference; MA: meta-analysis; MIDA: migraine disability assessment; MD: mean difference; MPS: mean pain score; NNT: number needed to treat: NP: neuropathic pain; NRS: Numeric rating scale; NSAIDs: non-steroidal anti-inflammatory drugs; P: p-value; PD: pain difference; PDN: painful diabetic neuropathy; PGB: pregabalin; PHN: postherpetic neuralgia; PI: pain intensity ; PS: pain score; PTNP: post-traumatic neuropathic pain; RCT: randomised controlled trials; REM: random effect model; RR: Risk Ratio; SAE: serious adverse events; SIS: sleep interference scale; SMD: standardized mean difference; SNRIs: selective norepinephrine reuptake inhibitors; SR: systematic review; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants; TID: three times daily; VAS: visual analogue scale; vs: versus ; WOMAC: Western Ontario and McNaster Universities osteoarthritis index; WPI: widespread pain index.

1.4 Prescribing trends of gabapentin and pregabalin

Gabapentinoids are commonly prescribed to treat various conditions discussed earlier in this chapter. Over the past decade, there has been a significant increase in the prescription of gabapentinoids in many countries, including the United Kingdom. The rising prescription rates could potentially elevate the likelihood of misuse, abuse, poisoning, and death (Eguale et al., 2016). These concerns may prompt recommendations for stricter regulation and oversight in prescribing gabapentinoids (Bradley, 2016; PHE, 2014).

According to US national prescribing statistics, gabapentin was the country's tenth most prescribed drug in 2016, rising from 39 million prescriptions in 2012 to 64 million in 2016 (Pauly et al., 2020; IQVIA, 2018). The prevalence of gabapentin and pregabalin use increased significantly from 1.2% in 2002 to 3.9% in 2015, with a yearly increase of 10% (OR = 1.10 per year; 95% confident interval (CI): 1.09–1.11; $P < 0.001$) (Johansen, 2018). Gabapentin was the most prescribed gabapentinoid, with 82.6% of patients using it (95% CI: 81.0%–84.2%) (Johansen, 2018). Prescription patterns for gabapentin also displayed a notable increase, with the number of participants per 1000 beneficiaries rising from 13.3 to 27.1 between 2009 and 2016 (Pauly et al., 2020). A recent analysis of US pain medication prescriptions indicated an increase in gabapentinoid prescriptions from 13.2% in 2014 to 19.0% in 2018 (Gorfinkel et al., 2022).

A study analysing administrative health records in Manitoba, Canada, reported a significant increase in gabapentin use among non-epileptic users. The usage rose from 0.2 per 1000 in the first quarter of 1998–1999 to 11.1 per 1000 in the final quarter of 2012–2013 (Leong et al., 2016). In Germany, a cross-sectional longitudinal study

conducted from 2009 to 2015 found that 1.3% of insured individuals received at least one prescription for pregabalin or gabapentin. There was an increase in prevalence from 1.1% in 2009 to 1.6% in 2015 (Viniol et al., 2019). Moreover, the annual incidence of prescriptions for pregabalin and gabapentin rose from 0.6% in 2010 to 0.7% in 2015 (Viniol et al., 2019). In Australia, a population-based retrospective cohort analysis revealed a significant rise in pregabalin dispensing between 2013 and 2016, with an annual increase of 73,424 prescriptions (Cairns et al., 2019). Lastly, in Finland, a study examined the prevalence of gabapentin and pregabalin use in nursing homes and assisted living facilities. The prevalence in nursing homes increased from 0.6% in 2003 to 4.8% in 2011, and in assisted living facilities, it grew from 2.2% in 2007 to 7.4% in 2011 (Pitkälä et al., 2015).

In the UK, the number of prescriptions for gabapentin and pregabalin increased by 46% and 53% respectively between 2011 and 2013, rising from 2.65 million to 4.9 million for gabapentin and from 1.55 million to 3.3 million for pregabalin (PHE, 2014). A study utilising the Clinical Practice Research Datalink (CPRD) revealed that pregabalin was prescribed to 1.1% of patients, while gabapentin was prescribed to 2% of the patient population, totalling 12,512,468 individuals (Montastruc et al., 2018). The rate of new users of gabapentin therapy increased annually from 230 per 100,000 individuals in 2007 to 679 in 2017. Similarly, the rate for pregabalin therapy escalated from 128 to 379 per 100,000 individuals per year in the same period (Montastruc et al., 2018). The annual incidence rate of first-time prescriptions for gabapentinoids rose from 1.6 per 1000 person-years in 2000 to 27.6 in 2015 (Appleyard et al., 2019). The number of prescriptions for gabapentinoids in England and Wales increased significantly from 1 million to 10.5 million between 2004 and 2015 (Lyndon et al., 2017).

According to National Health Service (NHS) England, the number of prescription items for pregabalin increased 7.6-fold from 2008 to 2018, from 919,456 to 6,997,715, and gabapentin prescriptions also expanded 4.2-fold, from 1,755,810 to 7,362,388, within the same period (NHS Digital, 2018b). A retrospective examination of government data revealed an increase in the median rate of prescriptions for gabapentin and pregabalin per 1000 people in England from 2013–2014 to 2017–2018 (GBP = 83.6 to 136.2; PGB = 65.8 to 118.6) (Green et al., 2019). Cross-national research utilising Prescription Cost Analysis (PCA) datasets from 2010 to 2019 showed variations in gabapentinoid usage across the UK nations, all exhibiting an overall upward trend (Kurdi, 2021). Wales had the largest increase in gabapentinoid prescribing per 1,000 people at 285.8%, followed by England at 233.8%, Scotland at 223.6%, and Northern Ireland at 126.5% (Kurdi, 2021). Rahman et al. (2021) observed a significant rise in the incidence rate of gabapentin prescriptions between 2007 and 2017 in the United Kingdom. In England, the rate rose from 212 to 617 per 100,000 person-years, while in Scotland, it increased from 369 to 742, in Wales from 268 to 728, and in Northern Ireland from 139 to 836. The annual incidence rate of prescriptions for pregabalin also increased: from 118 to 351 in England, from 96 to 418 in Scotland, and from 104 to 370 in Wales. Northern Ireland's rate initially rose from 546 to 1139 between 2007 and 2010 but then declined to 532 in 2017 (Rahman et al., 2021).

1.5 Safety Issues with pregabalin and gabapentin utilisation

1.5.1 Risk of gabapentinoids misuse, overdose, and abuse

The misuse or improper utilisation of prescription medications is a widespread global phenomenon that poses a significant public health issue. According to the World

Health Organisation (WHO) (WHO, 2006), drug misuse or abuse is defined as using a substance for purposes that do not align with legal or medical standards. This behaviour has adverse consequences for an individual's functioning or health, and in severe cases, it can lead to death. The Advisory Council on the Misuse of Drugs (ACMD) (ACMD, 1998) characterises drug abuse in the United Kingdom as a state that has the potential to result in social, psychological, physical, or legal issues due to intoxication, frequent excessive use, and/or the development of a dependency on drugs.

Analgesic usage contributes to drug misuse worldwide and is frequently reported as one of the most commonly abused substances (NCDAS, 2022; Ritchie et al., 2018). Death rates associated with the misuse of highly addictive drugs, such as opioids, are clearly on the rise (Bastiaens et al., 2016; McNamara et al., 2015). According to the Director of the National Institute on Drug Abuse in the US, most individuals use prescription pharmaceuticals safely. However, over 50 million Americans (20% of those aged 12 and older) have used them for non-medical purposes at least once (Volkow, 2011). The National Centre for Drug Abuse Statistics reports that 9.7 million people aged 12 years and older abuse medications, including opioids (NCDAS, 2022). Approximately 16.5% of these substance abusers first abuse analgesics, making them the most commonly abused class of prescription medications (NCDAS, 2022).

Over the last decade, pregabalin and gabapentin misuse has become a major concern. Gabapentinoids are increasingly abused and misused, as indicated by several epidemiological studies. A study conducted in Sweden examined pregabalin-related AEs in drug abuse or addiction cases and found that pregabalin usage was involved in 16 of 198 cases (8%) (Schwan et al., 2010). In a study utilising the French Pharmacovigilance Database, 1.5% (n = 8) of 521 abuse or dependence cases

involved pregabalin (Bossard et al., 2016). Another study, conducted by the German Federal Institute for Drugs and Medical Devices, identified 55 instances of PGB misuse or dependency (Gahr et al., 2013). In Ireland, out of 1,489 reported poisoning deaths, 240 (16%) involved pregabalin (Lynn et al., 2020). Questionnaires administered in six Scottish drug abuse institutions revealed that of the 129 participants, 8% had been prescribed gabapentinoids, 22% had misused them, and 38% had misused them to enhance the effects of methadone (Baird, Fox, and Colvin, 2014). According to Irish research examining clinical and forensic toxicological data, gabapentinoids accounted for 2.9% of the 72,391 intentional drug overdoses (IDOs) recorded in emergency departments (Daly et al., 2018).

Pregabalin has a higher misuse potential than gabapentin due to its potency, bioavailability, and ability to induce euphoria (Chincholkar, 2020). EudraVigilance statistics show that pregabalin and gabapentin have been associated with adverse drug reactions (ADRs) related to misuse, abuse, and dependency. Specifically, pregabalin had 7,639 reports (6.6% of 115,616), while gabapentin had 4,301 (4.8% of 90,166) (Chiappini and Schifano, 2016). Another research determined that 576 (5.7%) of 10,038 gabapentin-related ADEs were abuse-related, and 58 (10.2%) of 571 pregabalin-related ADEs were abuse-related (Evoy et al., 2019).

According to Vickers-Smith et al. (2020), 26% of 97,813 pregabalin ADE reports were abuse-related, and 22.9% of 99,977 gabapentin reports were abuse-related. A retrospective examination of US electronic poison centre data found that of 347 cases, pregabalin and gabapentin overdoses accounted for 116 (33.4%) and 23 (6.6%) cases, respectively (Wills et al., 2014). French research utilising a large sample of beneficiaries revealed that 12.8% (n = 1,112) of 8,692 new pregabalin users and 6.6% (n = 130) of 1,963 new gabapentin users abused the medicine (Driot et al., 2019).

However, Kapil et al. (2014) conducted an online survey of 1,500 UK residents aged 16–59 years and found that gabapentin misuse was more prevalent than pregabalin misuse, with rates of 1.1% and 0.5%, respectively.

1.5.1.1 Risk factors associated with gabapentinoids use and abuse or misuse

To assess the long-term misuse potential of pregabalin and gabapentin, it is essential to better understand the risk factors. Healthcare providers must identify and monitor these risk factors to prevent misuse and overuse. These risk factors include a history of substance misuse particularly with opioids, psychiatric comorbidities, and concurrent use of other drugs such as benzodiazepines or sedatives. Additionally, factors such as multiple drug overdoses, gender, and age increase the risk of gabapentinoid abuse (Lyndon et al., 2017; Smith et al., 2012; Spence, 2013).

Opioid dependency and methadone usage have been identified as risk factors for gabapentinoid abuse. A French population study found that methadone-dependent individuals had an adjusted hazard ratio (HR) of 4.01 (1.49–10.81) for abusing pregabalin. In contrast, Driot et al. (2019) found no association between gabapentin abuse and methadone use. In a Swedish opioid maintenance therapy (OMT) clinic, 21% (16/73) of patients non-medically used pregabalin for psychological issues (65%) or recreational purposes (27%) (Dahlman et al., 2016). Questionnaire-based research at six drug addiction clinics found that 22% (29/129) of respondents used non-prescription gabapentinoids, while 100% (29/29) of them used methadone as prescribed for opioid dependency. Intoxication and methadone enhancement were effects of non-prescription gabapentinoid use (Baird et al., 2014).

Pregabalin usage was reported by 7% of patients in a US substance use disorder (SUD) clinic undergoing treatment for opioid addiction, whilst 22% of patients undergoing the same treatment reported gabapentin misuse (Wilens et al., 2015). Similarly, in Germany, 12.1% of patients with opioid addictions also abused pregabalin, compared to 2.7% of those with non-opioid addictions (Grosshans et al., 2013). An aggregated analysis from a systematic review by Evoy et al. (2017) revealed a higher rate of gabapentinoid abuse among opioid users, ranging from 3% to 68%, compared to 1.6% in the general population. In Finnish research, 43 gabapentin deaths and 316 pregabalin deaths were identified, with 48.1% related to pregabalin abuse and 18.6% related to gabapentin abuse (Hakkinen, 2014). Among the abuse cases, 91% of pregabalin abusers and 88% of gabapentin abusers also used opioids (Hakkinen, 2014). Multiple US studies interviewing patients have identified reasons for gabapentin misuse. These studies indicate that gabapentin is often used to enhance the effects of concurrently consumed substances, to experience euphoria, or to alleviate opioid withdrawal and physical pain (Applewhite et al., 2020; Buttram and Kurtz, 2021; Buttram, 2019; Vickers-Smith, 2018).

A current diagnosis or history of SUD is another factor that may contribute to the misuse, abuse, or overdose of gabapentinoids. In a study conducted in the United Kingdom, it was found that 1.0% (136 out of 13,480) of patients were taking a dose of pregabalin that exceeded the maximum approved dose (> 600 mg/day). Among these patients, 18.4% (25 out of 136) had histories of SUD, compared to 14% in the overall patient population (n = 13,480) (Asomaning et al., 2016). A Swedish study reported that 8.5% of 48,550 pregabalin users exceeded the maximum recommended dose (> 600 mg/day), and 31% of these patients had a history of SUD diagnosis or treatment (Boden et al., 2013). Research in the United Arab Emirates (UAE) focused on SUD

patterns among a first-time cohort selected from Abu Dhabi's National Rehabilitation Centre (NRC) found that the prevalence of simultaneous pregabalin misuse was as high as 68% (Alblooshi et al., 2016). A retrospective study by Evoy et al. (2019) concluded that pregabalin abuse was more prevalent among individuals who misused opioids and benzodiazepines.

Abuse of gabapentinoids is associated with the concurrent use of other illicit substances that depress the central nervous system, such as sedatives and antipsychotics. A Danish study reported that individuals taking antipsychotics and benzodiazepines were more likely to exceed the maximum prescribed dose of pregabalin (Schjerning et al., 2016). Research by the Irish National Drug Treatment Centre found that 9.2% (39 out of 440) of individuals receiving addiction services tested positive for pregabalin (McNamara et al., 2015). Only 10 (25.4%) of these 39 patients had been prescribed the medication. Among those who tested positive for pregabalin, 31.8% also had opiates in their system, 11.4% had cocaine, 79.5% had benzodiazepines, and 78% had cannabis (McNamara et al., 2015). A multidisciplinary study on gabapentinoid abuse amongst heroin users revealed that 70% (21 out of 30) used a gabapentinoid in conjunction with heroin. Of these, two used gabapentin and 19 used pregabalin (Lyndon et al., 2017). Participants reported that pregabalin was easily accessible and enhanced the effects of heroin. However, they expressed concerns about experiencing ‘blackouts’ and the risk of overdosing (Lyndon et al., 2017). Pregabalin was detected in 4.4% (43 out of 982) of post-mortem examinations conducted from 2010 to 2012 (Lottner-Nau et al., 2013), with each case involving additional illegal substances such as opiates/opioids, benzodiazepines, and antidepressants.

Gabapentinoid misuse is most common in younger age groups, specifically between 18 and 40 years. In a study analysing 359 post-mortem toxicological reports, the median age of individuals who abused gabapentinoids was 30 years, while the median age for non-users was 58 years (Hakkinen, 2014). Similarly, amongst 440 patients with SUD, the median age of pregabalin users was found to be 38 years (McNamara et al., 2015). The average age at the first instance of gabapentin misuse was reported to be 31.8 years (Buttram and Kurtz, 2021). However, In the French population, a younger age range (18–45 years) was associated with a significant incidence of gabapentinoid abuse, with a HR of 2.04 (95% CI: 1.71–2.45) for pregabalin and 2.27 (95% CI: 1.44–3.57) for gabapentin (Driot et al., 2019). Furthermore, in a Swedish cohort, patients aged 18–29 years were identified as being at risk of receiving doses of pregabalin exceeding 600 mg/day (Boden et al., 2013).

Data regarding gender disparities in gabapentinoid misuse or abuse are inconsistent. A post-mortem toxicological investigation revealed that 73.3% of individuals who abused pregabalin were male (Gahr et al., 2013). Similar findings emerged from Danish research on drug use, which indicated that males were significantly more likely to exceed the maximum daily dose of pregabalin (Schjerning et al., 2016). However, contrasting results suggest that females are more prevalent in cases of gabapentinoid abuse. An analysis of the EudraVigilance database, which focused on ADRs related to gabapentinoid abuse/misuse/dependence, found a higher number of female cases. Specifically, there were 5,765 female cases compared to 1,872 male cases for pregabalin and 2,913 female cases compared to 1,387 male cases for gabapentin (Chiappini and Schifano, 2016). According to a study examining a cohort of opioid users, women misused gabapentin significantly more than men, with a percentage difference of 17.3% (95% CI: 10.4–24.6%) (Smith et al., 2015).

The presence of mental health comorbidities is a significant contributing factor to the abuse or misuse of gabapentinoids. A study using a written questionnaire analysed the non-medical use of drugs among 250 former prisoners living in correctional community centres. It found that 62% (n = 155) admitted to non-medical drug use, with 16% (n = 24) specifically reporting gabapentin misuse (Bastiaens et al., 2016). The most commonly indicated mental health problems among these individuals were depression and Attention-Deficit Hyperactivity Disorder (ADHD). Additionally, 26% of individuals with opioid use disorders (OUD) (n = 145) reported abusing gabapentin, compared to 4% of those without OUDs (n = 105) (Bastiaens et al., 2016). Another study assessed the use of psychiatric medication in patients admitted to a public detoxification programme through a self-report survey. Of the 196 admissions, which included 162 people with opioid dependence, 85% had at least one psychiatric diagnosis, and 21% were using psychotropic medications (Wilens et al., 2015). This study found that 36% of patients taking psychiatric drugs reported abusing gabapentin, while 50% reported abusing pregabalin (Wilens et al., 2015).

1.5.2 Mortality associated with pregabalin and gabapentin

The risks of mortality associated with gabapentinoids have received significant attention and research. Although they are generally considered safe when used as prescribed, there have been reports of adverse outcomes, including fatalities, linked to misuse, abuse, and overdose (Kurdi, 2021; Evoy et al., 2017). A retrospective, register-based analysis utilising data from the Swedish national registry found that pregabalin significantly increased the risk of overdose death (HR 2.82, 95% CI: 1.79–4.43) in patients receiving OMT (Abrahamsson et al., 2017). This study also associated a two-fold increase in all-cause death with pregabalin use (HR 2.01, 95% CI: 1.38–2.91) (Abrahamsson et al., 2017). An Australian study, utilising post-mortem

coronial reports, observed an increase in the detection of pregabalin, from 2.8% in 2015 to 5.8% in 2017. Additionally, high rates of concurrent opioid (79%) and benzodiazepine (70%) use were noted in cases involving pregabalin (Thompson et al., 2020). In Finland, a retrospective cohort investigation into medicolegal deaths discovered gabapentin in 2.9% and pregabalin in 29% of 786 fatal poisoning cases (Haukka et al., 2018). Pregabalin was implicated in 2.3% (316 cases) and gabapentin in 0.3% (43 cases) of 13,766 fatalities between 2010 and 2011 (Hakkinen, 2014).

Multiple studies in the US have explored mortality rates related to gabapentinoid use. One retrospective analysis disclosed a rising involvement of gabapentin in drug overdose fatalities, increasing from 2.9% (30 cases) in 2013 to 17% (185 cases) in 2014. In these gabapentin-involved cases, the concurrent detection of alprazolam, benzodiazepines, and opioids was common, accounting for 41% (Hargrove et al., 2018). Another retrospective review identified gabapentin in 22% (931 out of 4169) of overdose cases. Out of the total number of individuals who were found to have opioids in their system, 26% (880 out of 3360) were also found to have gabapentin, indicating significant variations in its detection across various states and legal areas ($p<0.0001$) (Slavova et al., 2018a). Additionally, gabapentin was directly implicated in 47.1% (49 out of 104) of deaths, with at least one opioid present in 77.6% of these cases (Tharp et al., 2019). However, a retrospective database review of patients on OMT found that the use of gabapentinoids was associated with a significantly increased risk of mortality from all causes by 70% (HR = 1.71, 95% CI: 1.33–2.20), but not specifically from drug-related poisoning (HR = 1.54, 95% CI: 0.60–3.98; p = 0.373) (Macleod et al., 2019).

According to the Office for National Statistics in the United Kingdom, there were 4,561 drug-related fatalities reported in England and Wales in 2020 (ONS, 2021a). PGB and

GBP have been linked to increased fatalities in 2020, with a 41% increase (from 244 to 344 deaths) and a 32.6% increase (from 89 to 118 deaths), respectively (ONS, 2021a). Figure 1-2 shows the number of gabapentinoid-related deaths from 2010 to 2020. Since 2012, the rate has been rising annually; however, the increase from 2019 was not statistically significant (ONS, 2021a). Data from the National Records of Scotland indicate that there were 1,339 drug-related fatalities in Scotland in 2020, with 502 (37%) attributed to gabapentin and pregabalin. The number of gabapentinoid-related fatalities in Scotland saw an increase of 283.2%, from 131 in 2015 to 502 in 2020 (NRS, 2021).

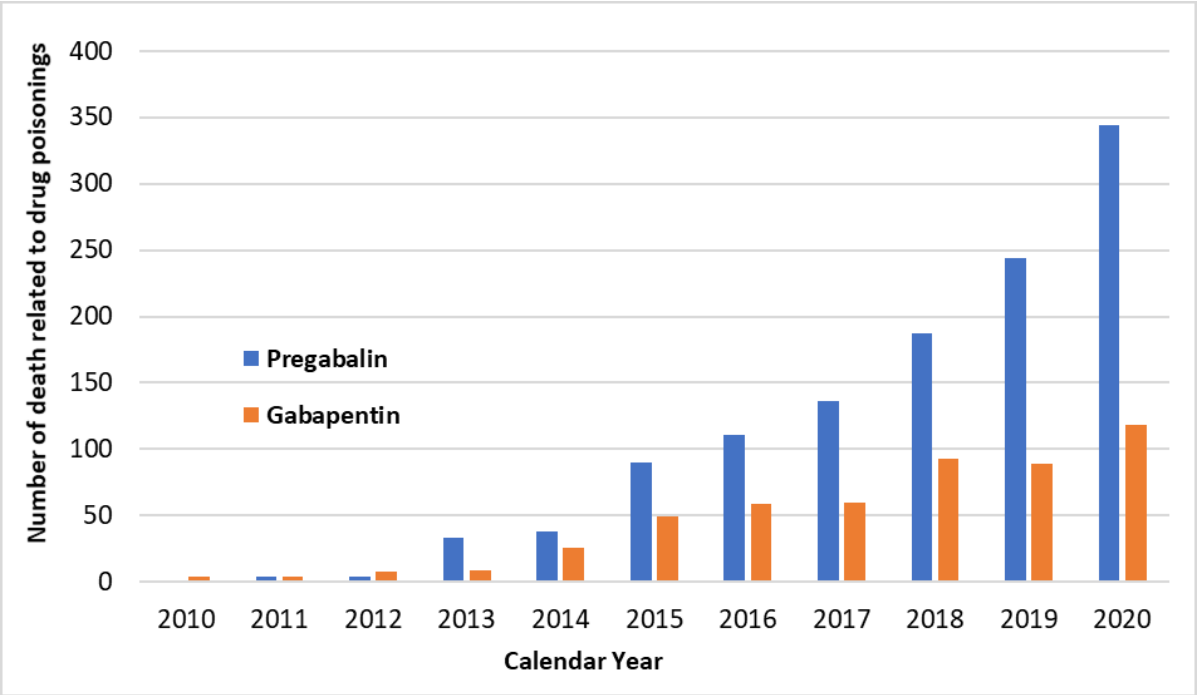


Figure 1-2: Number of Gabapentinoid Deaths Related to Drug Poisoning in England and Wales, Deaths Registered between 2010 and 2020

Note: Adapted from office for national statistics (ONS), 2021. "Deaths related to drug poisoning by selected substances, England and Wales." Retrieved from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsrelatedtodrugpoisoningbyselectedsubstances.

Research on gabapentinoid-associated deaths in the United Kingdom has been limited. A total of 316 fatalities have been reported due to pregabalin overdose. In

these cases, postmortem analysis revealed a significantly elevated blood concentration of pregabalin at 15 mg/L, in contrast to the normal reported concentration of 5.8 mg/L (Launiainen and Ojanperä, 2014). Elliott et al. (2017) analysed 93 postmortem cases, finding that 71 were directly related to drugs, with a median blood level of pregabalin at 7.0 mg/L. In contrast, 13 deaths due to other causes had a median concentration of 2.6 mg/L. In cases where PGB was a major cause of death, the median concentration reached 57.0 mg/L, ranging from 28 mg/L to 182 mg/L (Elliott et al., 2017). Another forensic toxicology study in Ireland examined the national Drug Related Death (DRD) index and found pregabalin in 16% (240 out of 1489) of toxicology reports between 2013 and 2016, with a significant increase over the years (Lynn et al., 2020).

A UK-based study reported an increase in annual fatalities associated with gabapentinoids, totalling 137 deaths in 2015. In these cases, opioids accounted for 79% (Lyndon et al., 2017). Another investigation in the UK focused on gabapentin and pregabalin-related polydrug deaths. Out of 3,750 samples, 118 (3.1%) tested positive for gabapentin and 229 (6.1%) for pregabalin. Heroin users were 4.1 times more likely to take pregabalin (19.5%) compared to non-users (4.7%) ($P < 0.0001$) (Nahar et al., 2019). In Tayside, Scotland, gabapentinoids were implicated in 39% of drug-related fatalities in 2016, with the majority involving non-prescription medications (Torrance et al., 2020).

These findings underscore the potential risks associated with gabapentinoids, emphasising the importance of appropriate use, monitoring, and education about the potential dangers of misuse and overdose. Healthcare professionals should remain vigilant in assessing the risks and benefits of prescribing gabapentinoids, particularly in patients with a history of SUD or other comorbidities.

1.6 The reclassification of pregabalin and gabapentin as controlled drugs

The increased number of gabapentinoid prescriptions, both licensed and unlicensed, has raised concerns about their potential for misuse, abuse, and poisoning. This is particularly true when used in combination with other substances such as opioids, which are linked to increased deaths. In many countries, pregabalin and gabapentin have been reclassified as controlled drugs. In 2014, Public Health England (PHE) responded to the rising illicit use of gabapentin and pregabalin by issuing guidance to prescribers about the risks of abuse (PHE, 2014). Subsequently, in 2016, the ACMD recommended that GBP and PGB be classified as Class C restricted substances under the Misuse of Drugs Act 1971 (Bradley, 2016). In 2019, the UK government reclassified gabapentin and pregabalin as Class C Schedule III controlled substances to better manage their potential for misuse, abuse, and related deaths (GOV.UK, 2018). The reclassification of pregabalin and gabapentin as controlled drugs meant that their prescribing, dispensing, and storage became subject to stricter regulations and monitoring.

1.7 Summary of the literature review

Gabapentin and pregabalin are typically prescribed as adjunctive therapy for epilepsy, the management of neuropathic pain, and generalised anxiety disorder. These medications have also undergone clinical trials to test their efficacy and safety profiles in treating conditions such as chronic LBP, fibromyalgia, headache, migraine, and musculoskeletal and joint pain. An analysis of clinical trials aimed at determining the efficacy of either pregabalin or gabapentin showed that these medications were effective for several pain conditions such as diabetic neuropathy, PHN, and

fibromyalgia. However, there is limited evidence supporting the use of gabapentinoids for chronic LBP, headache, migraine, and musculoskeletal joint pain. The SEs reported with gabapentin and pregabalin were primarily moderate and included sleepiness, dry mouth, dizziness, and peripheral oedema.

Although gabapentin and pregabalin have been associated with several health benefits in treating different pain conditions, it is essential to consider their safety and tolerability, given their potential for misuse and abuse. In addition, the mortality rates associated with gabapentinoids have increased among individuals who misuse or abuse them. Several risk factors predispose individuals to gabapentinoid abuse or misuse, particularly those previously diagnosed with a substance use disorder, such as opioids or illicit drugs. Studies have shown that the increased mortality rate due to gabapentinoid misuse is correlated with opioid misuse. Therefore, physicians need to carefully consider the potential harms of these drugs when prescribing them, and policymakers must take into account the potential for illegal use and the risks of misuse and abuse.

The increasing prescription of gabapentinoids in the UK has been associated with a rising number of deaths. This emerging concern has led to the reclassification of both compounds as Schedule 3 controlled substances. Developing strategies to limit the availability of these drugs is crucial in reducing the mortality rate amongst at-risk or vulnerable populations. It is essential to gain a clear understanding of the role of gabapentinoids in pain management, as well as their potential harms, including misuse and abuse. This understanding is necessary to comprehend the reasons for their classification as controlled drugs and to assess the potential impact of this reclassification on prescription patterns, possible harms, and associated deaths.

1.8 Rationale, research aims, and objectives

The 2019 reclassification of GBP and PGB as controlled substances in the United Kingdom spurred the initiation of this doctoral study. It is crucial to investigate the prescribing trends of gabapentinoids and their associated risks, including overdose and death, as well as the impact of this policy change on their use in patients with chronic pain diagnoses. Such an examination could help optimise gabapentinoid prescribing practices and improve pain management. Additionally, the findings may provide valuable insights that could inform evidence-based practices and guide future policy decisions.

Despite the high prevalence of chronic pain, there is limited data on prescribing PGB and gabapentin for such conditions. Population-level patterns of gabapentinoid use in chronic pain patients remain inadequately described, with few studies investigating changes in prescribing trends over time. Additionally, research using longitudinal data to examine gabapentinoid use for managing various pain conditions in the United Kingdom—including neuropathic pain, back pain, fibromyalgia, headaches, migraines, and musculoskeletal and joint pain—is scarce. The reasons for the increased use of gabapentinoids in chronic pain patients, as well as the impact of their reclassification on usage, have yet to be thoroughly examined. Furthermore, there is a notable absence of epidemiological studies on the safety of gabapentinoid usage in chronic pain patients, specifically concerning overdose and all-cause mortality. Most existing literature on gabapentinoid overdose and mortality has relied solely on post-mortem toxicological analysis, resulting in a limited understanding of potential risk factors such as patient demographics, comorbidity history, substance abuse, and concurrent use of other substances like opioids, sedatives, antidepressants, and z-drugs.

For these purposes, this PhD project aims to investigate the prescribing trends and dose patterns of gabapentinoids in the chronic pain population, evaluate the effect of the reclassification of gabapentinoids on drug utilisation, and optimise the safety of drug use (particularly concerning overdose) and mortality within this population in UK primary care. To address these identified knowledge gaps, the study sets the following specific objectives:

(1) To describe the prescribing trends of gabapentinoids and the dosing pattern for patients with chronic pain conditions.

(2) To determine the range of chronic pain conditions treated with gabapentinoids, including both neuropathic pain (licensed) and other non-neuropathic chronic pain (unlicensed).

(3) To evaluate the impact of gabapentinoid reclassification on their use in patients with chronic pain diagnoses.

(4) To compare the recording of overdose events between CPRD and HES databases.

(5) To examine the association between gabapentinoid use and the risk of overdose in patients with a chronic pain diagnosis using primary care and secondary care databases.

(6) To compare the recording of death events between CPRD and ONS databases.

(7) To evaluate the association between gabapentinoid use and all-cause mortality in patients with chronic pain diagnosis using primary care and ONS mortality statistics.

Chapter 2: Methodology

2.1 Introduction

This chapter provides a comprehensive overview of the methods employed in this research. It offers detailed descriptions of the methods used in four distinct studies: (1) Trends and patterns of gabapentinoid utilisation, (2) The impact of gabapentinoid reclassification, (3) The association between gabapentinoid use and the risk of overdose, and (4) The association between gabapentinoid use and all-cause mortality. It outlines the research design, data sources, data extraction processes, the methodology utilised to select the participants, the outcomes, and the statistical analysis. The chapter also addresses ethical considerations and discusses the measures taken to ensure the validity and reliability of the research findings. Through a systematic presentation of the methods, this chapter sets the foundation for the subsequent results and discussions.

2.2 Methodological overview of the studies within the presented research

This section describes the methodologies employed in each study individually, providing a detailed account of the procedures and analyses utilised

2.2.1 Study 1: trends and patterns of gabapentinoid utilisation

2.2.1.1 Study design

A repeated cross-sectional observational study was conducted from 1st January 2005 to 31st December 2020 to analyse the prescribing trends and dosing patterns of gabapentinoids in chronic pain management and identify the chronic pain conditions

(licensed and unlicensed) treated with gabapentinoids. This time period was chosen to mitigate potential issues arising from poor recording in the early stages and suboptimal data recording prior to pregabalin's approval for pain treatment in 2004.

2.2.1.1.1 The rational for selecting repeated cross sectional design

The repeated cross-sectional observational approach was chosen to identify trends and patterns in gabapentinoid utilisation due to its distinct advantages in capturing population-level changes over time. This methodological design allows for the collection of data at multiple time points, which is crucial for observing temporal variations in medication use. By repeatedly sampling different cohorts from the same population, this approach can effectively identify shifts in prescribing behaviours, patient demographics, and utilisation patterns without the need for long-term follow-up of the same individuals (Levin, 2006; Setia, 2016).

This design also minimises the potential biases associated with loss to follow-up, which is a common issue in cohort longitudinal studies (Caplan et al., 1995; Wang & Cheng, 2020). Overall, the repeated cross-sectional observational approach provides a reliable and efficient framework for examining the dynamic trends and patterns of gabapentinoid use, thereby offering valuable insights into the evolving landscape of medication utilisation in the UK.

2.2.1.2 Data source

The CPRD was the primary data source for investigating the research inquiries. It is a major electronic health database in the United Kingdom, managed by the Department of Health and funded through a partnership between the National Institute for Health Research (NIHR) and the Medicines and Healthcare Products Regulatory Agency (MHRA) (Herrett et al., 2015). Established in 1987, the CPRD contains anonymised

records from over 60 million patients, with 16 million active contributors (i.e., those who are alive, currently registered, and actively providing data) from more than 2,000 general practices, representing the UK's diverse demographic profile in age, gender, and ethnicity. As of January 2021, 394 of the 8,961 practices contribute actively to CPRD GOLD, encompassing records for over 3 million active patients out of nearly 19.5 million acceptable patients (i.e., those deemed to have a 'research-quality' record), including patients who have been transferred out or deceased (CPRD, 2021b).

Data are collected from General Practices (GPs) using the Vision system, provided by In Practice Systems Ltd. (INPS). These data are gathered daily during routine clinical visits with patient consent. Each patient is assigned a unique NHS identification number to document all interactions. GPs submit data monthly, recording illnesses, new symptoms, and key clinical events such as diagnoses, test results, referrals, and hospital admissions (Herrett et al., 2015). Clinical events should be reported in the database under three specific scenarios: at initial diagnosis, when a change in treatment is required, or upon occurrence of a major event like a referral (Jordan et al., 2007).

Moreover, the database organises its information into ten distinct files: patient, staff, clinical practice, consultation, therapy, immunisation, referral, test, and additional files, summarised in Table 2-1. Each file uses a unique patient identifier (patid), except the practice file, which uses a practice identification number. The patid, an encrypted combination of patient and practice IDs, links records across all ten files (CPRD, 2019).

Table 2-1: Summary of Types of Files and Associated Data in the CPRD

File Type	Content
Patient	Represents the specific characteristics of the patient and details relevant to their registration.
Practice	Accounts for relevant practice details, such as information collection and specific region.
Staff	Contains practice staff details, with one record per member of staff.
Consultation	Holds information about the consultation type the GP enters from pre-determined lists. It includes events from the consultation process via the consid.
Clinical	Represents all medical history events, including data on medical history such as signs, symptoms, and diagnoses, entered into the GP system.
Additional Clinical details	Carries structured data entered through the GP software. This means that a patient could have more than one data row, as the data is connected to the clinical file events through the adid.
Referral	Contains all details of referrals made through the GP system. The information includes details of patient referrals to secondary care facilities (often to other care settings such as hospitals that offer inpatient or outpatient care), as well as the specialty of the referral.
Immunisation	Contains details of immunisation records on the GP system.
Test	Holds records of test data on the GP system.
Therapy	Contains information about every prescription on the GP system. This file provides information on all prescriptions (drugs and appliances) issued by the doctor.

adid: additional details identifier; consid: consultation identifier; GP: General practice

Detailed internal assessments are conducted on all incoming data to ensure accuracy, completeness, validity, and logical coherence. These assessments include practice-level evaluations that grant an 'up-to-standard' (UTS) status to practices, indicating their data are suitable for research. Patient data are deemed 'acceptable' if they show internal consistency in age, gender, registration, and event records. The database routinely checks aspects like weekly consultations and prescriptions, demographic

accuracy, and causes of death. Practices must document 95% of prescriptions and patient events to meet research criteria. Data failing to meet standards are excluded from the database (Herrett et al., 2015).

The CPRD effectively links primary-level patient data through the Health and Social Care Information Centre (HSCIC) to secondary care datasets. As of August 2019, the CPRD GOLD linking database included patient information from 416 clinics, representing about 74% of CPRD GOLD practices in England and 50% across the UK. This linkage extends to several datasets, including cancer registration, hospital admissions, and mortality data. For this study, data were linked to the Hospital Episode Statistics (HES) for inpatient care and the Office for National Statistics (ONS) mortality datasets, ensuring comprehensive support for the research aims and objectives (CPRD, 2021a).

2.2.1.2.1 Rationale for the selection of CPRD as a primary data source

The CPRD was chosen as the main data source for several reasons. First, it hosts a comprehensive database from over 2,000 UK primary care practices, representing 50 million patients, with 16 million actively contributing. Notably, 25% of these patients have been followed for at least 20 years, enabling thorough epidemiological studies and accurate statistical evaluations (CPRD, 2019). The longitudinal data are valuable for analysing drug usage trends, patterns, and long-term outcomes, aligning with this thesis's aims. CPRD accurately reflects the UK's demographic characteristics, representing approximately 4.52% of the total UK population (ONS, 2021). Validation studies have demonstrated CPRD's high data quality and validity, with a median of 89% verified diagnoses across 183 conditions (Herrett et al., 2010). Finally, CPRD can link with HES and ONS data, broadening the scope of accessible data and increasing the statistical power of studies (Padmanabhan et al., 2019).

2.2.1.3 Study population

The selection of the study population involved several steps, including the identification of pain diagnosis codes, the identification of gabapentinoid (pregabalin and gabapentin) codes, and then methodologies and procedures employed in the selection of the study population.

2.2.1.3.1 The identification of pain diagnosis codes list

The identification of patients with neuropathic and non-neuropathic pain (including fibromyalgia, back pain, musculoskeletal joint pain, migraines, and headaches) was established using the Read/Med code system. Read codes are a comprehensive, semi-hierarchical clinical classification system developed by Dr. James Read in the early 1980s for Electronic Health Records (HER) usage (Booth, 1994). As the primary coding system for clinical data in the UK, they capture over 80,000 clinical terms in GP practices, standardising terminology for patient care and treatment discussions (Booth, 1994; NHS Digital, 2016). This system allows clinicians to categorise pain using symptom-based, diagnosis-based, or combined approaches when documenting pain in EHRs. Neuropathic and non-neuropathic pain can be documented in EHRs using specific terms. For example, musculoskeletal joint pain can be recorded as peripheral osteoarthritis-related symptoms like knee pain or arthralgia. Specific diagnoses such as knee OA can also be included (Jordan et al., 2016).

A diagnosis-based definition with strict selection criteria decreases sensitivity but increases specificity, making it suitable for recruiting patients in treatment trials. In contrast, a symptom-based definition, which is clinical in nature, is more sensitive and identifies more cases but with lower specificity, making it useful for studies identifying all necessary cases (Shrestha et al., 2016; Yu et al., 2017; Jordan et al., 2016). For example, a UK study using CPRD data estimated OA incidence with both definitions.

In 2013, the clinical OA incidence rate was 47.7 per 1000 person-years (95% CI, 47.4 to 47.9), while diagnosed OA was 7.9 per 1000 person-years (95% CI, 7.8 to 8.0) (Yu et al., 2017).

This research selected patients with neuropathic and non-neuropathic pain using diagnostic or combined symptom and diagnostic definitions to balance sensitivity and specificity. The process began with generating lists of READ/Med terms related to each pain type, which were then used to find the relevant READ/Med codes in the CPRD GOLD medical browser dictionary (Table 2-2). These lists were combined with codes from relevant article supplements and a clinical codes repository from the University of Manchester (https://clinicalcodes.rss.mhs.man.ac.uk). Duplicate entries were then eliminated from the final list (Appendix II).

Table 2-2: READ/Med Code Lists for Each Chronic Pain Condition

Pain condition	Type of pain definition	READ/Med terms	Source of pain code list
Neuropathic pain	Diagnosis based	*neuropathy*, * neuralgia*, * stenosis*, and * Sciatica*	Gajria et al., 2011
Back pain	Diagnosis and symptom based	* back pain*, *Backache*,*back*,*lumbar* and *back stiffness*	Doran et al., 2011
Musculoskeletal joint pain	Diagnosis and symptom based	*arthritis*, *osteoarthritis*, *arthrosis*, * rheumatoid*, *knee pain*, *joint pain* and *ankyloses*	Jordan et al., 2007 and Kontopantelis et al., 2015
Fibromyalgia pain	Diagnosis based	*Fibromyalgia* and * fibrositis*	Collin et al., 2017
Migraine and headache pain	Diagnosis based	*migraine* and *headache*	Gorton et al., 2021 and Masefield et al., 2022

2.2.1.3.2 The identification of gabapentinoid (pregabalin and gabapentin) codes list

The drug list for pregabalin and gabapentin was produced by using the product dictionary items within the CPRD GOLD online system's 'product browser'. This method was used to produce a list of product codes for pregabalin and gabapentin. Appendix III contains the list of prod codes for pregabalin and gabapentin.

2.2.1.3.3 Selection of the staniudy population

The study population comprises patients diagnosed with chronic pain who have been prescribed GBP and PGB. Figure 2-1 summarises the identification process for the study population.

Patients diagnosed with pain were identified using a predefined list of pain medcodes (READ codes) from the 'define tool' in the CPRD GOLD database between 1993 and 2020 (Appendix II). Records before the 'up to standard practice date' were excluded. The 'up to standard practice date' indicates abnormalities based on mortality rate and data collection consistency.

To confirm a chronic pain diagnosis, patients needed at least two consecutive codes for the same pain diagnosis separated by at least 90 days, or a medcode term that includes 'chronic'. Patients with only a single pain diagnosis, unless termed 'chronic', were excluded to avoid including acute pain diagnoses. Cancer pain patients were also excluded (Appendix IV). Patients diagnosed with chronic pain before 2004 were excluded to ensure a temporal sequence between the chronic pain diagnosis and gabapentinoid prescription.

The procedure to identify gabapentinoid users with chronic pain diagnoses is summarised in Figure 2-1. Prescription records of gabapentinoids (pregabalin and

gabapentin) were identified using a pre-generated prodcode list (Appendix III). Patients prescribed gabapentinoids were identified by applying the prodcode to the 'define tool'. This list was then merged with the list of patients diagnosed with chronic pain using the unique patid to identify gabapentinoid users with chronic pain.

Prescriptions recorded before the 'up to standard practices date' were excluded. Patients diagnosed with epilepsy (Appendix V) were also excluded to reduce false positives and ensure gabapentinoids were prescribed for chronic pain. The epilepsy diagnoses list was determined by applying specific medcodes to the 'define tool' within CPRD GOLD. Prescriptions issued before 1st January 2005 were excluded. Patients with unreported gender and those under 18 at their first gabapentinoid prescription on the index date (1st January 2005, to death, end of registration, or 31st December 2020) were also excluded.

To identify the chronic pain indications corresponding to patients' first gabapentinoid prescription within the study period, relevant diagnostic codes were used with time restrictions from one year prior to six months post-prescription (-365 to +180 days) (Figure 2-1). This was done to ensure that any medical diagnosis documented in the CPRD database was captured. The diagnosis dates remain unchanged until subsequent occurrences like the first diagnosis, medication initiation, patient transfer, or referral (Jordan et al., 2007). Since there is no direct link between prescriptions and their exact indications in the CPRD, this study used a methodology from previous research to infer chronic pain indications for each gabapentinoid prescription (Appleyard et al., 2019; Montastruc et al., 2018). The approach specifically examined the date of chronic pain diagnosis within one year before or six months after the first gabapentinoid prescription (Appleyard et al., 2019; Montastruc et al., 2018).

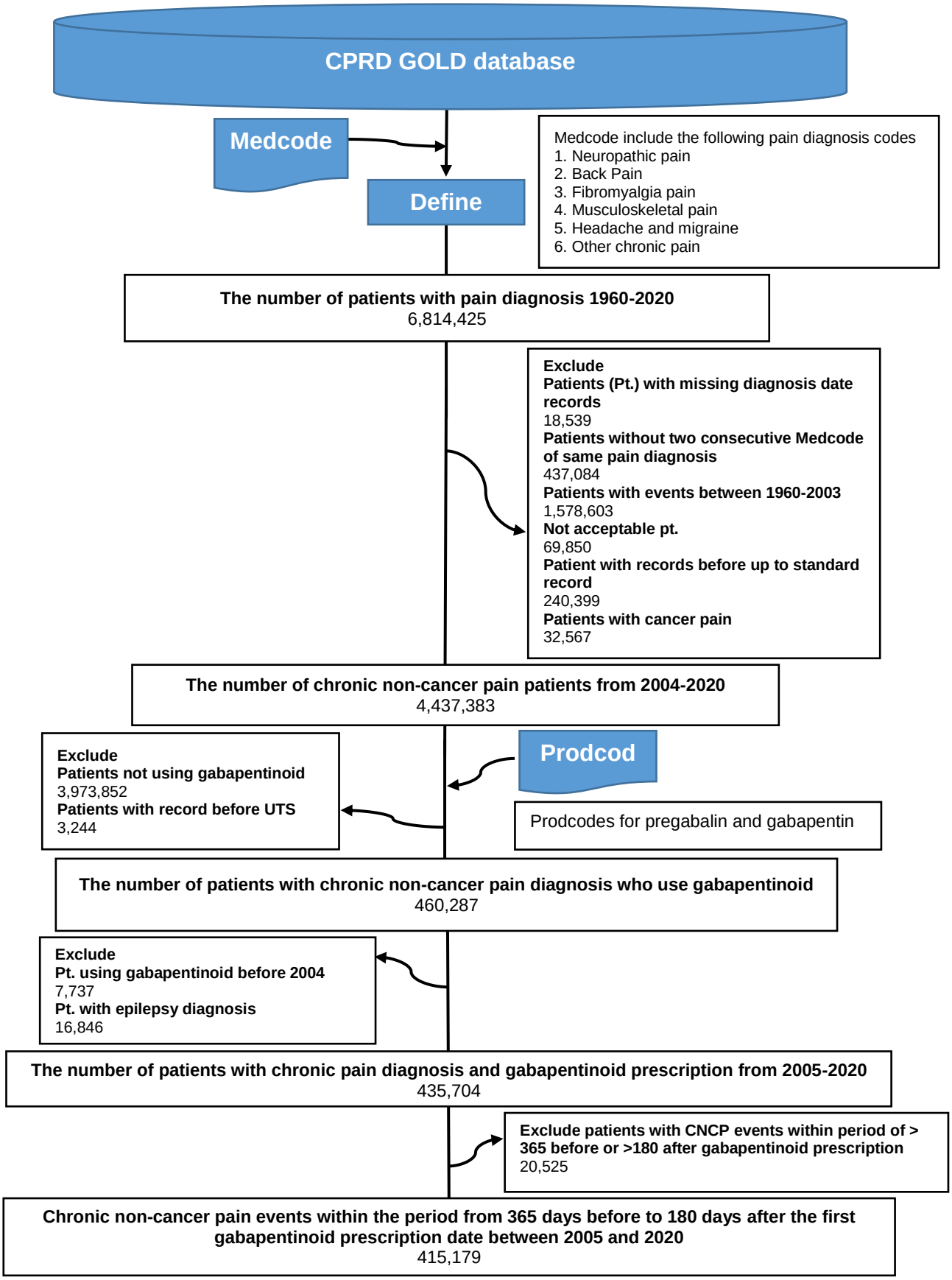


Figure 2-1: The Procedure to Identify Overall Population List of Gabapentinoid Users with Chronic Pain Diagnoses

2.2.1.4 Follow up period

The follow-up period commences from the most recent of the following dates: 1st January 2005, the UTS date, or the current registration date (crd) (i.e., the date when the patient's current period of registration with the practice starts). The observation was continued until the earliest of the following dates: 31st December 2020, the transfer-out date, the last collection date in the CPRD, or the date of death.

2.2.1.5 Outcome measures

The study outcome measures were calculated individually for each drug (pregabalin and gabapentin) within each calendar year.

2.2.1.5.1 Number of pregabalin and gabapentin prescriptions

The annual measure of prescriptions for pregabalin and gabapentin was recorded from January 2005 to December 2020. Within each calendar year, the number of prescriptions per 1000 registrants in the CPRD database was calculated.

2.2.1.5.2 Annual prevalence of pregabalin and gabapentin users

The annual prevalence of PGB and GBP users between 2005 and 2020 was calculated by dividing the number of patients prescribed pregabalin or gabapentin calendar year (numerator) by the total number of CPRD registrants for that year (denominator). This ratio was then multiplied by 10,000 to determine the number of patients prescribed these drugs per 10,000 CPRD registrants. Patients who received prescriptions in multiple years were counted as users for each respective year, resulting in multiple inclusions. The measures used were derived from prior research on drug use prevalence (Aarts et al., 2014).

2.2.1.5.3 Annual incidence of pregabalin and gabapentin users

The annual incidence of individuals using pregabalin and gabapentin was assessed over the period spanning from 2005 to 2020. Incidence cases were characterised as individuals who had not been prescribed gabapentinoid medication in the preceding years. The calculation was performed separately for pregabalin and gabapentin. It involved dividing the number of new users in the calendar year (numerator) by the total number of adult CPRD registrants at risk in the same year (denominator). The outcome was then multiplied by 10,000 to determine the incidence per 10,000 CPRD registrants.

2.2.1.5.4 Chronic pain indications for pregabalin or gabapentin prescriptions

The identification of chronic pain conditions related to gabapentinoid prescriptions was performed using appropriate clinical codes within a specific timeframe, as explained in the previous Section (2.2.1.3.3) of this chapter.

2.2.1.5.5 Prescribed daily dose

The Prescribed daily dose (PDD) of pregabalin and gabapentin was determined annually using CPRD prescription records. PDD per user estimates the Average Daily Dose (ADD) of these drugs prescribed to chronic pain patients in primary care. The ADD was calculated by totaling the dose in milligrams (strength x quantity) for each patient over a calendar year. Then dividing by the number of users at same calendar year, and then dividing by the total number of patient days of supply. This method was adapted from studies by Coupland et al. (2018) and Venkateshwarlu et al. (2018).

2.2.1.5.6 Days' supply (DS)

The DS calculation involved dividing the total quantity (QTY) of gabapentin or pregabalin by the numeric daily doses (ndd), representing the number of tablets,

capsules, or milliliters prescribed, as documented in the CPRD therapy file. This value indicates how long the medication would last for a patient and was aggregated yearly (Coupland et al., 2018). If the period between consecutive prescriptions was shorter than the days covered by the previous prescription, the previous prescription's days were adjusted accordingly. Annual days' supply was capped at 365 days.

2.2.1.6 Data management

In this study, a comprehensive data management process was executed to ensure the accuracy, reliability, and integrity of the data, which are paramount for valid statistical analyses and meaningful research outcomes. The following section details the steps taken to clean, validate, and impute missing data, ensuring that the datasets used in these studies were of the highest quality.

The CPRD data files were acquired via the CPRD GOLD interface and securely stored on the University of Nottingham's secure disk server. These files, in compressed text format, included therapy, clinical, referral, consultation, additional patient, and practice records. The saved files were subsequently imported into Stata 17 (StataCorp LLC, 2020. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) for statistical analysis (StataCorp, 2017).

Data cleaning was conducted as a preliminary step before analysis. This involved identifying and treating outliers as missing data and validating key information such as gender and year of birth (yob). It was ensured that the first registration date (frd) at the practice was on or after the birth date, and the crd was validated to be on or after both the birth date and the frd. Additionally, the transfer-out date was confirmed to be on or after the frd. Records without a year of birth were excluded as age could not be

calculated. Similarly, records without a diagnostic date were excluded as the timing of the diagnosis could not be determined.

Prescriptions were included if they occurred on or after the UTS date. All extracted variable data were examined for missing information. Prescriptions without the recommended amount and QTY were excluded. Consequently, 14 prescriptions (2 for gabapentin and 12 for pregabalin) were excluded due to missing QTY. There were varying proportions of missing ndd in the prescription records: 1,599,431 out of 4,991,023 (32.05%) for gabapentin and 884,035 out of 3,885,872 (22.7%) for pregabalin.

The ndd value is essential for calculating research outcomes such as prescribed daily dose, medication duration, and prescription length. Imputing incomplete ndd data involved a step-by-step method to ensure optimal use of CPRD data, aiming for comprehensive and accurate ndd values, as used in drug utilisation study (Baker, 2016a).

Before imputation, implausible ndd values were adjusted. For instance, a recorded ndd value of 900 (implausible) with a strength of 300 mg was corrected to 3, indicating one 300 mg tablet taken three times daily. Out of 4,991,023 gabapentin prescriptions, 5,810 (0.12%) had implausible values, and among 3,885,872 pregabalin prescriptions, 6,826 (0.18%) had implausible values. These were corrected to their true values.

A five-step process was used to impute missing ndd information. Step 1 utilised dosage instructions from the prescription with the missing ndd, the most reliable method. Step 2 used ndd from a previous or future prescription of the same product for the same patient. Step 3 relied on the median ndd for the same product during the patient's follow-up, as shown in Figure 2-2.

Before imputation, the mean and median ndd for gabapentin were 3.3 and 3, respectively, and for pregabalin, 2.14 and 2. Among the five strategies, steps two and three had the highest imputation rates: 23.5% and 8.9% for gabapentin, and 18.4% and 4.1% for pregabalin. These imputations did not change the median or mean ndd for pregabalin but slightly increased the mean daily dose of gabapentin from 3.3 to 3.7. This indicates the reliability and suitability of the imputation strategies used.

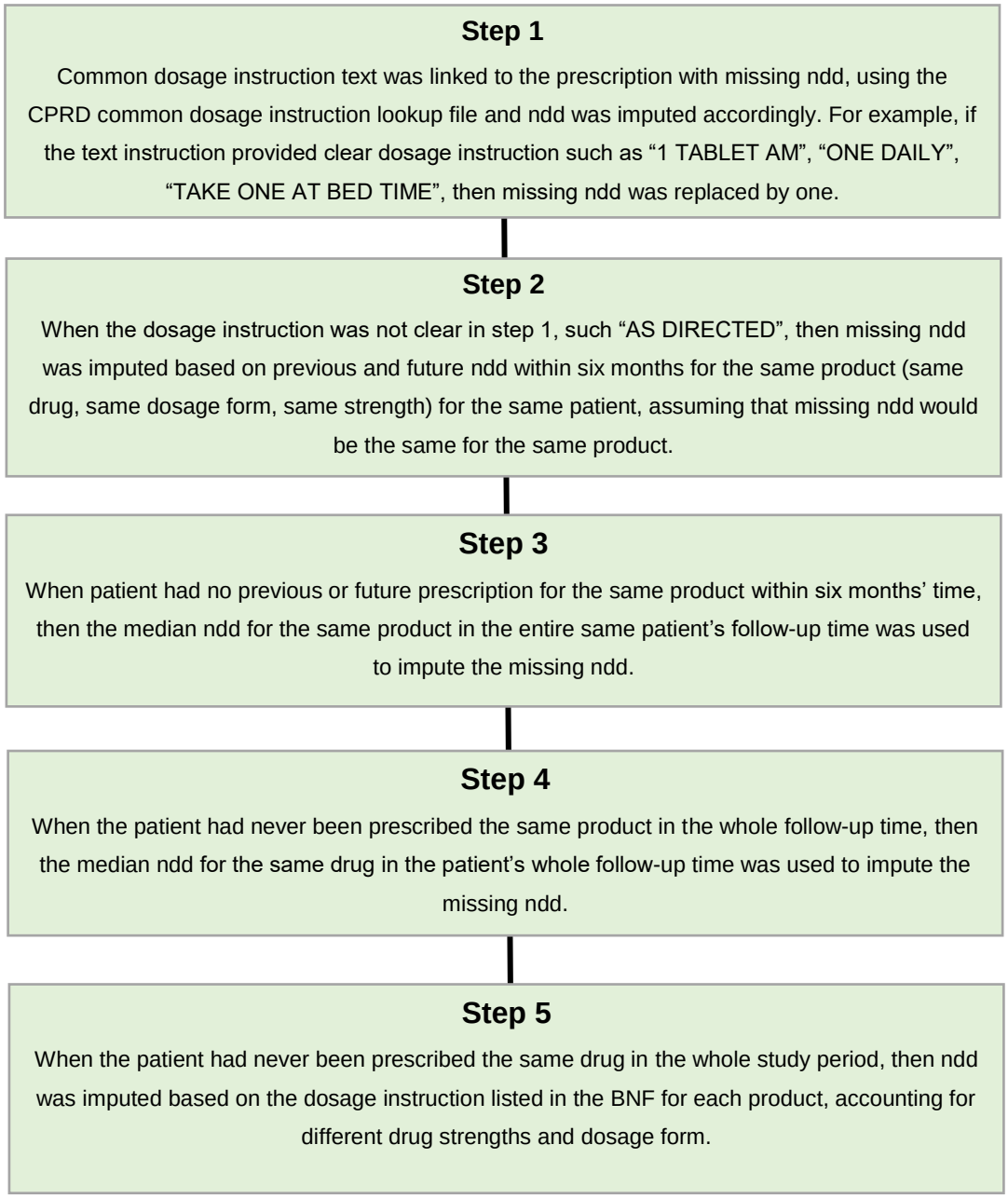


Figure 2-2: Steps for Imputing Missing ndd Based on Individual Patients' Data

2.2.1.7 Statistical analysis

A descriptive analysis was used to examine the demographics of gabapentinoid users, the frequency and percentage of gabapentinoid prescriptions among chronic pain patients, specific chronic pain diagnoses, and the average annual days' supply. The study drugs, pregabalin and gabapentin, were analysed by their annual prescriptions per 1000 CPRD registrants, with these trends plotted over the study period. The annual incidence and prevalence rates of gabapentin and pregabalin users per 10,000 registrants, as well as the annual prescribed daily dose per user, were reported from January 2005 to December 2020.

During the primary analysis, prescriptions were assigned to specific CNCP conditions if the corresponding chronic pain code was entered within a timeframe ranging from 365 days prior to the prescription date to 180 days after (+180 to -365). The analyses were conducted using STATA 17 software (StataCorp, 2017).

2.2.2 Study 2: the impact of gabapentinoid reclassification

2.2.2.1 Study design

To determine the effects of gabapentinoid reclassification on their usage among patients with chronic pain diagnoses, an observational study employing a cross-sectional quasi-experimental design was conducted between 1st August 2012 and 31st July 2020.

2.2.2.1.1 The rational for selecting quasi-experiments design

It was necessary to use the most suitable research design, in order to acquire reliable estimates of the outcome (the impact of drug reclassification on drug utilisation) (GOV.UK, 2021b). The most appropriate design was quasi-experiments such as before-and-after comparisons or time series analysis (GOV.UK, 2021b).

The primary difference between the two designs lies in their assessment approach. Before-and-after designs evaluate the impact of a policy twice: once before and once after implementation (GOV.UK, 2021b). In contrast, a time series design collects observations at multiple sequential time points before and after the policy is implemented (GOV.UK, 2021b). Many studies note the difficulty of attributing changes directly to a policy using the before-and-after method due to potential influences from other interventions (Hayes et al., 2015; McGovern et al., 2008; Millett et al., 2007). Thus, time series analysis is preferred for assessing policy effects on community practices. It is also recommended to monitor clinical activities in primary care for months or years before implementing a policy. This approach ensures that any observed changes are thoroughly assessed and not merely continuations of pre-existing trends (GOV.UK, 2021b; Wagner et al., 2002).

Time series designs include basic, control, and interrupted time series (ITS) (GOV.UK, 2021b). To assess the impact of gabapentinoid reclassification on drug utilisation patterns, ITS analysis was chosen (Wagner et al., 2002; GOV.UK, 2021b). ITS is used to measure intervention effects on specific outcomes, identify patterns leading to an intervention, and observe subsequent changes (Bernal, Cummins, and Gasparrini, 2017). This methodology examines outcomes before, during, and after the intervention, determining whether changes are temporary or sustained (Bernal et al., 2017; Wagner et al., 2002). Therefore, an ITS approach was selected to evaluate the effect of gabapentinoid reclassification on drug utilisation patterns before and after the April 2019 policy implementation.

2.2.2.2 Data source

The primary data source for this study was the CPRD. For detailed information, see Section 2.2.1.2 of this chapter. For the rationale behind selecting CPRD, refer to Section 2.2.1.2.1.

2.2.2.3 Study population

The process for selecting the study population and data extraction is detailed in Section 2.2.1.3 of this chapter. For this study, further exclusion was made due to the study period spanning (1st August 2012 to 31st July 2020). Patients with chronic pain (CP) events occurring from 365 days before to 180 days after the first gabapentinoid prescription date between 1st January 2005 and 31st July 2012 were excluded.

2.2.2.4 Follow up period

The study period extended from 1st August 2012 to 31st July 2020. This period was chosen to include significant events: the emergence of the first pregabalin abuse cases (2013), the publication of advice on the risk of gabapentinoid misuse (2014), and the release of the ACMD recommendation for reclassification (2016). These events collectively contributed to the reclassification of gabapentinoids (Millar et al., 2013; PHE, 2014; Bradley, 2016) (Figure 2-3).

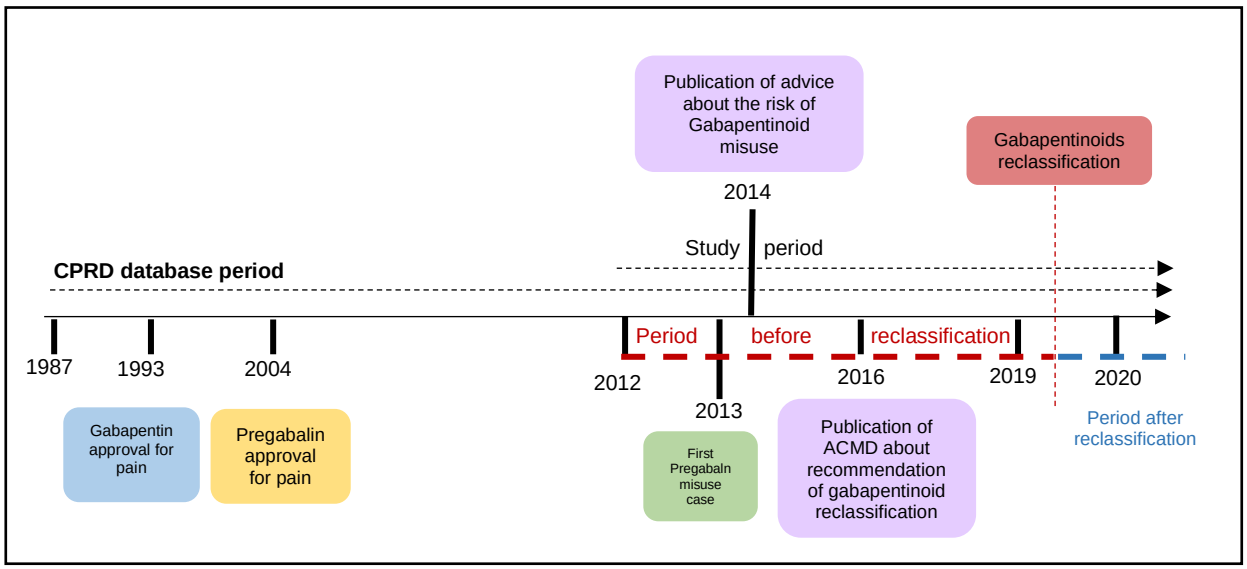


Figure 2-3: Time Line of the Important Events that Led to Gabapentinoid Reclassification

2.2.2.5 Outcome measures

The study aimed to estimate changes in the level and slope of the monthly prevalence of gabapentinoid users per 10,000 registrants and the trend of monthly gabapentin and pregabalin PDD per user. These measures used gabapentinoid prescription records from CPRD before and after the reclassification in April 2019. The monthly prevalence was calculated by adjusting the number of gabapentin or pregabalin users based on the monthly number of active CPRD patients. The PDD for each prescription was converted to monthly PDD to determine the prescribed daily doses per user. The procedure for determining PDD is outlined in Section 2.2.1.4.5 of this chapter.

To assess the sensitivity of gabapentinoid reclassification's impact on utilisation measures, we included additional time points corresponding to significant events mentioned in Section 2.2.2.1 (Figure 2-3). This analysis aimed to determine if these time points, along with reclassification, affected the monthly prevalence rate of gabapentinoid users.

2.2.2.6 Data management

Data cleaning and management procedures were conducted prior to conducting any analyses. These procedures were discussed in further depth in Section 2.2.1.5 of this chapter.

2.2.2.7 Statistical analysis

To evaluate the impact of gabapentinoid reclassification, an interrupted time series analysis with segmented regression was used. This method assessed changes in outcomes from CPRD data, specifically monthly PDD per user per day and monthly prevalence of gabapentinoid users per 10,000 registrants, both immediately after reclassification and over time.

Segmented regression requires consistent data at uniform intervals. It uses the time series of the targeted outcome to establish a baseline trend, which is then "interrupted" by an intervention at a specific point in time (Taljaard et al., 2014; Van Seben et al., 2016).

For this study, data were divided into two segments: before and after the intervention, with April 2019 marking the reclassification of gabapentinoids. This allowed for assessing trends in gabapentinoid usage before and after the policy implementation. A linear regression model, consisting of level and slope, was used to measure the variance between the segments. This approach allowed for evaluating changes in the prevalence and dosing patterns of gabapentin and pregabalin users before and after reclassification.

This study used a segmented multivariable regression model to calculate the level and trends in the monthly prevalence rate of pregabalin and gabapentin users per 10,000

registrants. It also calculated the monthly PDD before reclassification and the changes in level and trend after reclassification as follows:

Yt*= β0 + β1 * *time* + β2 * *gabapentinoids reclassification* + β3 * *time after gabapentinoids reclassification* + *et

Where ***Yt*** represents monthly gabapentinoid utilisation, measured as monthly PDD per user per day or monthly prevalence of gabapentinoid users per 10,000 registrants from CPRD. ***Time*** refers to time spans from the start of the observation period (1st August 2012) to the end (31st July 2020), measured monthly. ***Gabapentinoid reclassification*** is a binary variable: 0 before reclassification and 1 after, which occurred in the 81st month. ***Time after reclassification*** is a continuous variable counting months post-reclassification (from April 2019 to July 2020), coded as 0 before reclassification and (time-15) after.

In this model,

- ***β0*** is the baseline level of the outcome at the beginning of the series at time 0;
- ***β1*** is the baseline trend of monthly gabapentinoids utilisation before reclassification (i.e., slope);
- ***β2*** is the change in levels of monthly gabapentinoids utilisation immediately after the reclassification;
- ***β3*** is the change in the trend of monthly gabapentinoids utilisation after reclassification;
- ***et*** is an indicator of random error.

The time series has three characteristics: autocorrelation, non-stationarity, and seasonality, which can bias results (Lagarde and Palmer, 2011). First-order autocorrelation was tested using the Durbin-Watson test. Failure to correct for autocorrelation may overestimate intervention effects and underestimate standard

errors. Positive first-order autocorrelation was found in the gabapentin and pregabalin monthly prevalence time series. To correct this, two lags for the dependent variable were added to the model, and the Newey-West model was used for gabapentin prevalence to address autocorrelation and heteroscedasticity (NIST, 2012). The Dickey-Fuller Test identified seasonal unit roots and stationarity; the series is stationary if $P < 0.05$ (ESS, 2015; Turner et al., 2020).

Multiple regression assumptions were tested, including normality of residuals via graphical distribution analysis. Collinearity and multicollinearity among independent variables were checked using variance inflation factor (VIF) and tolerance measures. Heteroscedasticity of residuals was assessed with the Breusch-Pagan test.

STATA 17 was used for all analyses (StataCorp. 2017. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

2.2.3 Study 3: the association between gabapentinoid use and the risk of overdose

2.2.3.1 Study design

To investigate the link between gabapentinoid use and the risk of overdose in patients with a chronic pain diagnosis, a population-based cohort design using a within-individual approach (where participants served as their own controls) was utilised (Figure 2-4). The approach was based on Molero et al. (2019), which investigated associations between gabapentinoids and suicidal behaviours, accidental overdoses, motor vehicle accidents, injuries, and criminal violence in Sweden.

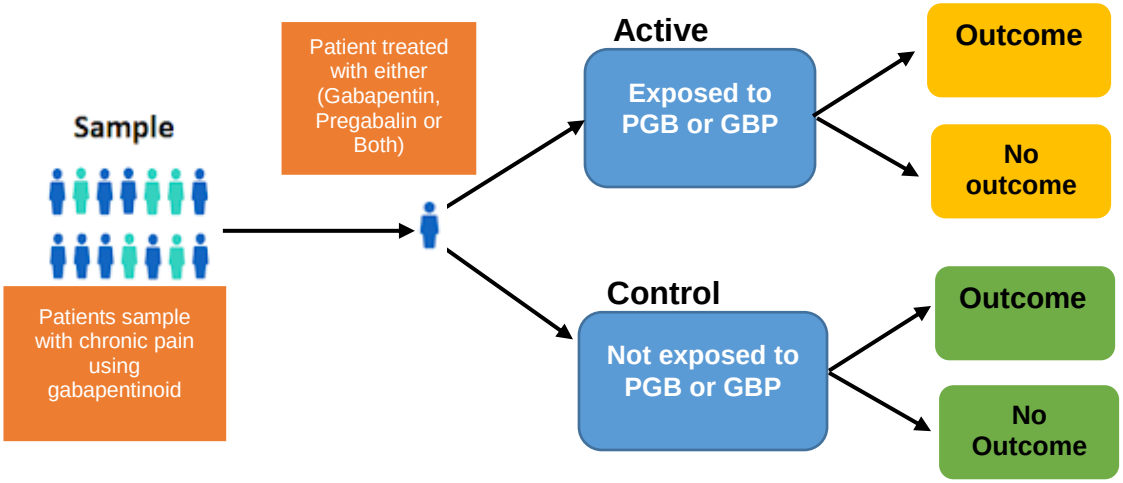


Figure 2-4: Cohort Study within Individual Design

2.2.3.1.1 The rational for selecting population-based cohort design using within individual approach

A population-based cohort design is a type of observational study that follows a group of individuals from a defined population over time to investigate the incidence and causes of disease or other health outcomes. This design allows researchers to examine associations between exposures (pregabalin and gabapentin in this study) and outcomes (overdose in this study) within the general population, providing a comprehensive understanding of the factors affecting health (Szklo, 1998).

The within individual approach was selected to accurately measure outcome occurrence over time, effectively addressing confounding by indication, and eliminating time-invariant confounding. This approach allows for exposure to all treatment levels, ensuring individual differences do not distort results (Molero et al., 2019).

2.2.3.2 Data source

This study utilised primary care records from the CPRD linked to secondary care records from the HES Admitted Patient Care (APC).

The HES database is managed by NHS Digital (formerly the Health and Social Care Information Centre). It contains comprehensive data on admissions to all NHS trusts in England, including Accident & Emergency (A&E) departments, primary healthcare trusts, and acute mental health centres. It captures all hospital admissions, outpatient consultations, and A&E visits, including data from private sector patients treated at NHS hospitals and non-residents treated at NHS-funded institutions (NHS Digital, 2018a). HES data support hospital payment processing and secondary uses like research. Access to HES data requires study protocol approval in line with data governance standards and research ethics (Herbert et al., 2017).

The HES database holds around 200 million records, categorised into hospitalisations, episodes, and events. A hospitalisation covers the period from a patient's admission to discharge, while an episode is when a patient is under continuous care from a single consultant. Since 1989, data on admitted patients have been collected systematically, with over 17 million consultant episodes added annually. In the financial year 2019/20, HES recorded 20.9 million APCs, up from 20.8 million the previous year (NHS Digital, 2018a, 2020b).

2.2.3.2.1 Rationale for the selecting linked CPRD to HES data for overdose

Intentional overdose is the most prevalent form of self-harm observed in hospital presentations in Ireland, the UK, Europe, and the US (Claassen et al., 2006; Hawton et al., 2007; Michel et al., 2000; Perry et al., 2012). These overdoses are typically managed in A&E, where the severity determines the need for hospital admission. NHS Digital (2021) reported 16,994 admissions in NHS hospitals in England in 2019/20 due to drug overuse-induced poisoning, a 9% increase from 2012/13 (15,580).

Most people in the UK are registered with primary care, where GP records serve as their primary medical records. Data is systematically gathered during routine clinical practice, with secondary-care information often shared with primary care physicians. However, delays, under-recording, or inaccuracies can occur when manually entering data into GP systems (McDonald et al., 2018). Many self-harm cases are not always appropriately recorded. For instance, GPs immediately recorded 32% of hospital-admitted self-harm incidents in the UK in 2012, and 68% within six months (Thomas et al., 2013). Poor documentation is confirmed by Herrett et al. (2013) and McDonald et al. (2018), who report significant under-recording of severe incidents like myocardial infarctions (MI) (21%) and significant bleeding episodes (80%). Inadequate GP documentation leads to under-recording and delays in primary care databases.

Linked datasets provide a more comprehensive health record by combining data from multiple sources. The impact of record linkage on capturing overdose episodes in patients using pregabalin or gabapentin is unclear. However, record linkage improves data accuracy and completeness in public health research (Thomas et al., 2013). Baker et al. (2016b) found that using linked data (CPRD, HES, and ONS) increased the incidence rate of injury (poisoning) by 26% compared to using primary care data alone. However, the study did not specify if the 'poisoning injury' data includes drug poisoning.

The overlap in overdose recording between the CPRD and HES databases is uncertain. Record linkage is essential for capturing differences in demographic and clinical features between primary and secondary care records. For example, CPRD data on suicide rates showed high rates in the elderly, while ONS indicated higher rates in younger age groups (Thomas et al., 2013). Additionally, CPRD recorded a 29% comorbidity prevalence, compared to 13% in HES data (Crooks, West, and Card,

2015). This discrepancy likely arises because primary care data provides ongoing clinical histories, while secondary care data offers limited snapshots of critical events. In summary, researchers emphasise the importance of linking primary care databases like CPRD with hospital records like HES for accurate outcome estimates.

2.2.3.3 Study population

The selection of patients and data extraction process was the same as process in Section 2.2.2.3. However, the patients within CPRD were linked to HES APC resulting in a final cohort of 106,129 patients after linkage.

2.2.3.4 Follow up period

The follow-up period started from the date of the initial gabapentinoid prescription within the study period (1st August 2012 to 31st July 2020) (Figure 2-5). The end of the follow-up period was marked by the earliest of the following dates: the date of death, the transfer-out date, the practice's last collection date, or the end of the study period on 31st July 2020.

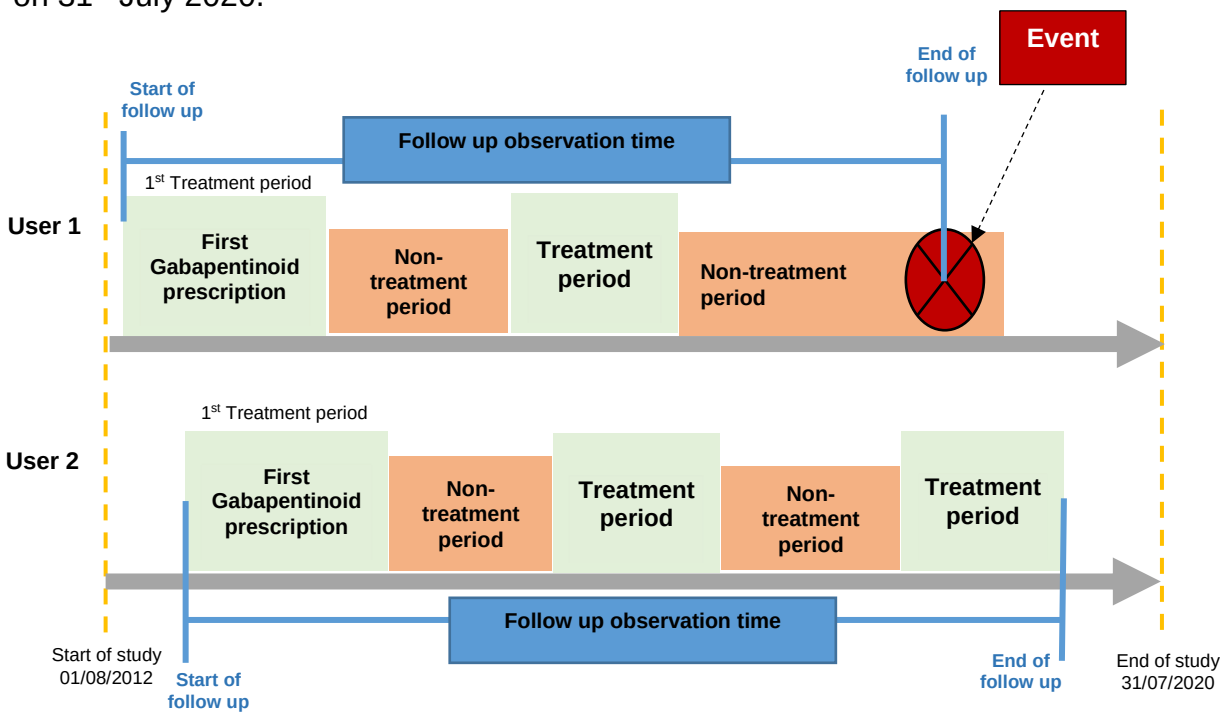


Figure 2-5: Illustration of the Follow-up Period for Each Patient

2.2.3.5 Exposure

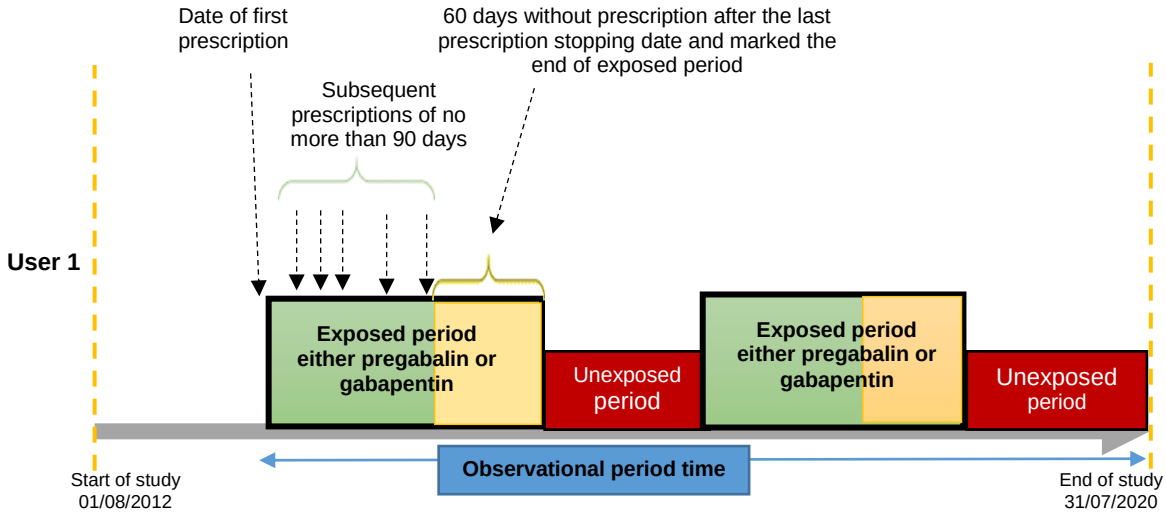
The primary exposure was the prescription of gabapentinoids (pregabalin and gabapentin). Patients were stratified into three mutually exclusive groups based on their gabapentinoid prescriptions during the follow-up period (Table 2-3). Product codes were used to identify gabapentinoid prescriptions in the therapy file (Appendix III).

Table 2-3: Treatment Groups According to the Prescribed Gabapentinoid

Gabapentinoid treatment groups	Description of Included Patients
Pregabalin group	Patients who were prescribed only pregabalin for chronic pain
Gabapentin group	Patients who were prescribed only gabapentin for chronic pain
Both group (gabapentinoid group)	Patients who were prescribed pregabalin and then switched to gabapentin, or vice versa

All follow-up time was divided into exposed and non-exposed periods. The exposed period was defined as having at least two consecutive prescriptions with no more than 90 days between them, plus an additional 60-day period to account for delays in prescription initiation, tablet accumulation, or outcomes within the withdrawal period. Gaps following gabapentinoid use were classified as non-exposed periods (Figure 2-6).

A) Pregabalin or gabapentin only group



B) Both group or gabapentinoid group

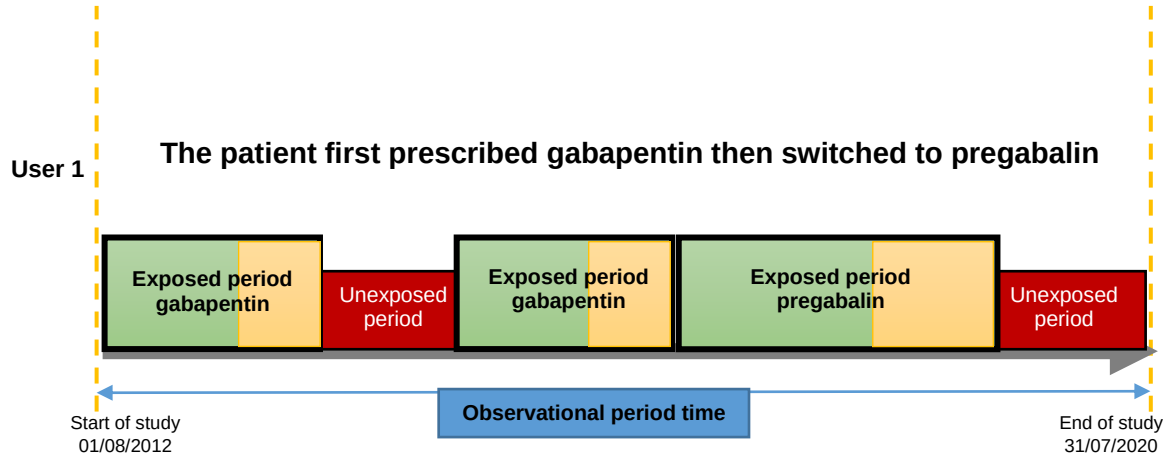


Figure 2-6: Illustration of Exposed and Non-Exposed Periods of Within-Individual Study Design

To assess the sensitivity of a 60-day post-prescription period, repeated measures were conducted with varying definitions of the end of an exposed period, including extending it to 90 days or reducing it to 30 days after the last prescription.

2.2.3.6 Time-varying (survival time definition)

The survival time for each patient was calculated by summing the days in all exposure periods during the study. Similarly, the non-exposed survival time was the sum of days in all non-exposed periods. Figure 2-7 illustrates this calculation.

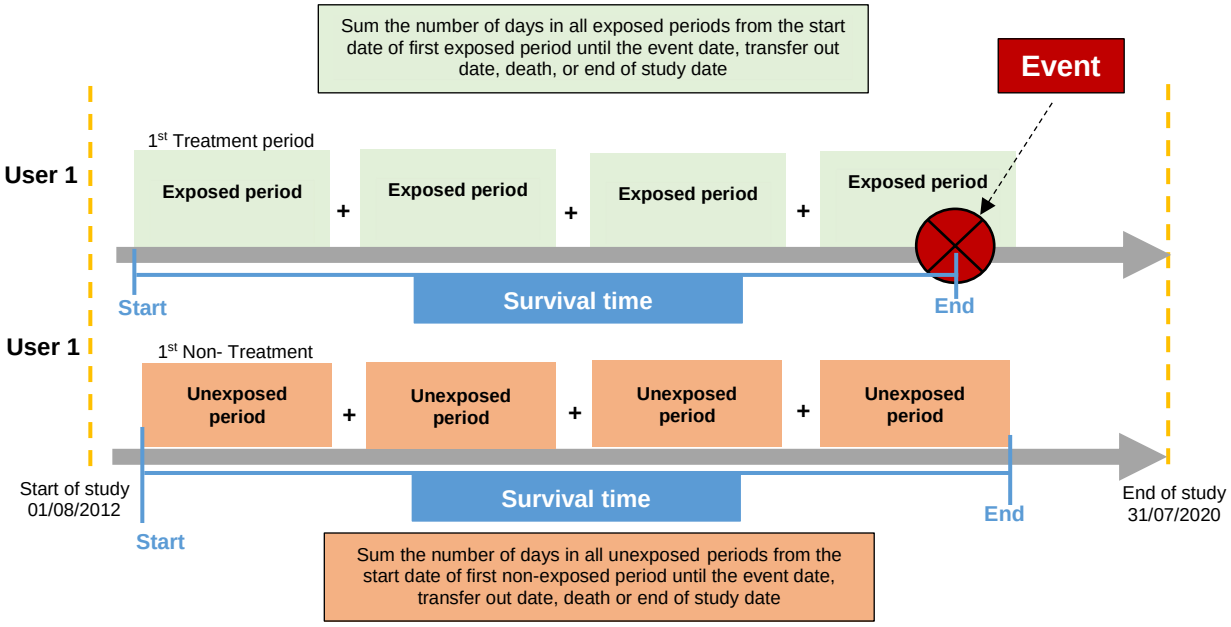


Figure 2-7: Illustration of the Survival Time Calculation for Each Patient

2.2.3.7 Outcome measures

2.2.3.7.1 Number and proportion of overdose events in CPRD, HES or both

During the research period, the number and percentage of patients with an overdose record in CPRD, HES APC, or both were identified and grouped accordingly. Table 2-4 provides definitions and related patient groups. Figure 2-8 illustrates the approach used. For patients with overdose records in both databases, the earliest recorded date was used for analysis.

Table 2-4: Operational and Practical Definitions of Patient Groups According to Overdose Records in CPRD, HES or Both Databases

Patient group	Operational definition	A practical definition of the patient group
Group 1 (CPRD only)	Patients who had an overdose recorded only in the CPRD (no overdose recorded in HES data).	Patients who may have had an overdose and then presented to A&E but whose cases did not require hospitalisation.
Group 2 (HES only)	Patients who had an overdose recorded only in HES data (no overdose recorded in CPRD).	Patients who had an overdose that required hospitalisation (severe cases).
Group 3 (Both databases)	Patients who had an overdose recorded in both the CPRD and HES databases.	Patients with an overdose record recorded in both primary care and hospital records.
Group 4 (Censored observations)	Patients who had no overdose record in either CPRD or HES data	Patients who did not have an overdose during the study in either database: no GP record or hospitalisation record for an overdose.

A&E: accident and emergency; CPRD: Clinical Practice Research Datalink; HES: Hospital episode statistics; GP: general practice

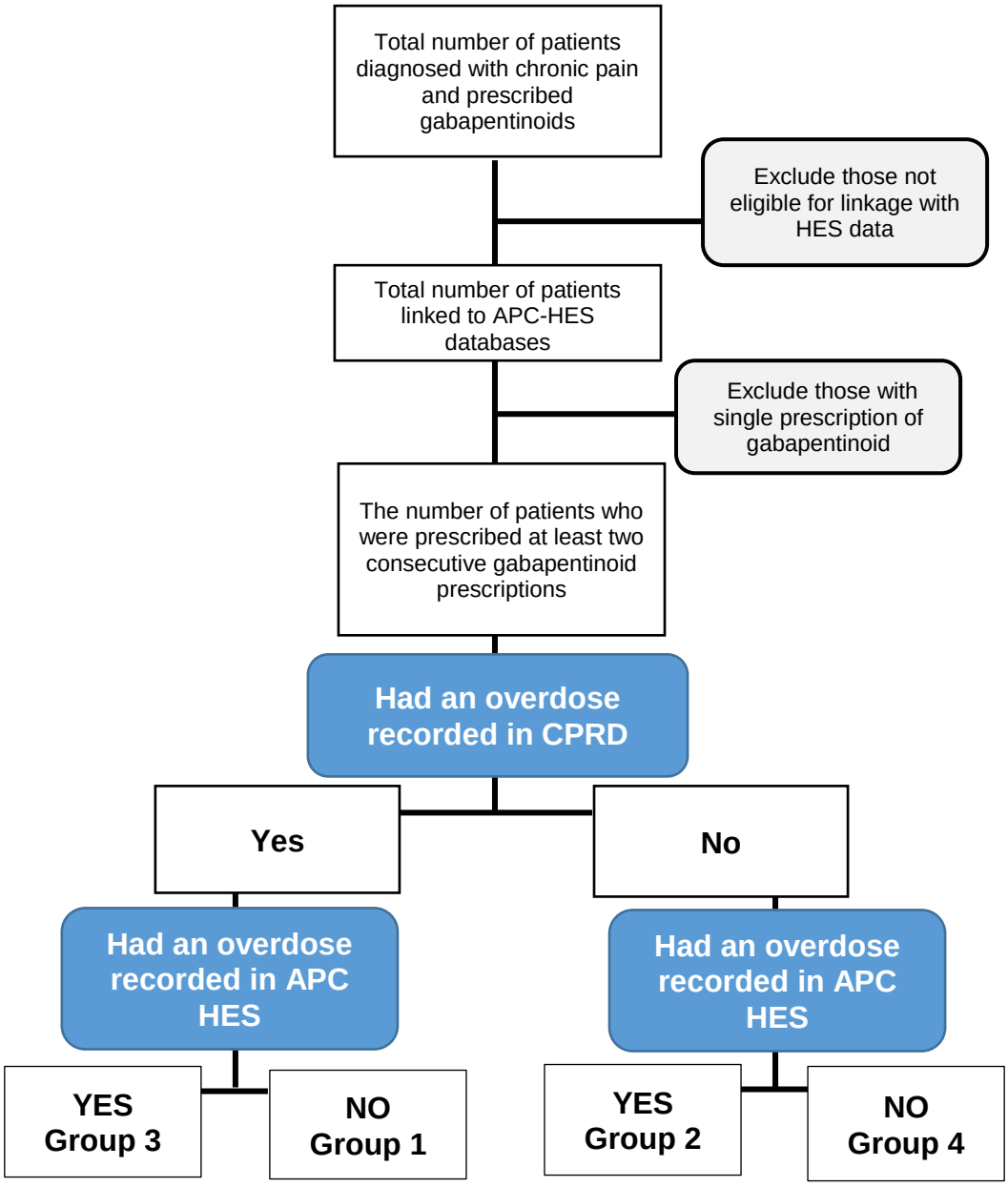


Figure 2-8: Flow Diagram Outlining the Process of Patient Group Identification According to the Existence of Overdose Case

2.2.3.7.2 Comparison of dates of overdose recording in both database

For patients in Group 3 (i.e., those with a record of an overdose in both the CPRD and HES APC databases), the earliest overdose date recorded in either database was identified, followed by the calculation of the gap in days between the two dates. If the patients had multiple overdose events recorded in one database, the difference between the first overdose date detected in that database and all subsequent

overdose dates from the other database was calculated. This step was essential to determine which overdose date corresponded to the first overdose event. The selected overdose date was the one with the smallest difference between the two dates. Finally, the gap (number of days) between these two dates was used to classify and categorise patients, as illustrated in Table 2-5. This methodology for categorisation was adapted from Gribbin's (2013) work on the incidence of falls in primary care.

Table 2-5: Time Gap between Overdose Recording Dates in CPRD and HES Datasets: Category and Definition

Time Gap Category	Definition
No gap	Overdose dates in CPRD and HES were recorded on the exact same date.
Very short gap	If the gap between the overdose dates recorded in CPRD and HES was less than or equal to 2 days.
Short gap	If the gap between the overdose dates recorded in CPRD and HES was more than 2 days but less than or equal to 7 days.
Intermediate gap	If the gap between the overdose dates recorded in CPRD and HES was more than 7 days but less than or equal to 14 days.
Long gap	If the gap between the overdose dates recorded in CPRD and HES was more than 14 days but less than or equal to 30 days.
Prolong gap 1	If the gap between the overdose dates recorded in CPRD and HES was more than 30 days but less than or equal to 60 days.
Prolong gap 2	If the gap between the overdose dates recorded in CPRD and HES was more than 60 days but less than or equal to 90 days.
Prolong gap 3	If the gap between the overdose dates recorded in CPRD and HES was more than 90 days.

CPRD: Clinical Practice Research Datalink; HES: Hospital episode statistics

2.2.3.7.3 Overdose Events

The primary outcome was the first overdose recorded within the study period. The primary outcome was the first overdose recorded within the study period. Overdose events were identified using Read and International Classification of Diseases, version

10 (ICD-10) codes. A Read code indicating an overdose in the clinical or referral files marked a patient as having experienced an overdose in the CPRD database. The Read code list was derived from the CPRD code browse and was cross-referenced with lists from published studies for accuracy and confirmed through correspondence with primary authors or supplementary documents (Carr et al., 2016; Thomas et al., 2013). Duplicate codes were removed to create a final list. Overdose-related hospital episodes in HES-APC records were identified using ICD-10 codes from previous research (Molero et al., 2019; WHO, 2016). Only the first overdose recorded after starting gabapentinoid prescriptions was evaluated; subsequent events were excluded. The Read and ICD-10 codes are in Appendix VII.

2.2.3.8 Potential confounding variables

The following baseline variables were measured for each patient during the year prior to the start of gabapentinoid prescription during the study period:

- Age: in years at the start of treatment (pregabalin or gabapentin).
- Gender: male or female.
- Deprivation score (as defined by the Index of Multiple Deprivations (IMD) quintiles): This measures residential area deprivation across seven aspects, including financial status, job availability, health deficits, disability, education and training opportunities, access to housing and services, crime, and living environment quality.
- Patients with a history of SUD as defined by the Read codes included in Appendix VIII.
- The use of other medicines (benzodiazepines, opioids, z-drugs, and antidepressants) was assessed 12 months before starting gabapentinoid

treatment to measure baseline parameters and ensure the inclusion of the most recently prescribed drugs. These drugs were identified using CPRD ‘Prod codes’ in the therapy file, listed in Appendix IX.

- Comorbidities such as depression, coronary heart disease (CHD), diabetes, stroke, anxiety, and chronic obstructive pulmonary disease (COPD) were assessed for one year before starting gabapentinoid prescriptions using appropriate Read codes from clinical, consultation, and referral files. Codes were sourced from the Quality and Outcomes Framework (QOF) business rules and the Cambridge 2018 version 1 code lists. This one-year period ensures updated comorbidities, as patients with chronic conditions typically visit their GPs annually. The Read codes used are listed in Appendix X.

A priori confounders known to affect the outcome based on previous literature, such as medications that increase overdose risk (opioids, benzodiazepines, z-drugs, and antidepressants) and comorbidities, were included in the final adjusted model (Evoy et al., 2021a; Peckham, Fairman, and Sclar, 2018b; Schofield et al., 2021).

2.2.3.9 Data management

Data inspection for missing information or outliers was conducted before analysis, as discussed in Section 2.2.1.5. HES files in .txt format were imported into STATA 17 for analysis. Date irregularities, such as discharge dates preceding admission dates or episode start dates after discharge dates, were detected and removed from the analysis.

2.2.3.10 Statistical analysis

Descriptive analysis was used to determine the proportion of patients with recorded overdose cases in the CPRD, HES databases, or both, and to compare the dates of overdose cases recorded in both databases.

The study used Cox proportional hazards regression to assess the association between overdose risk and pregabalin or gabapentin exposure. Gabapentinoid exposure was treated as time-varying, accounting for treatment initiation, discontinuation, or switching during follow-up. For example, a patient starting pregabalin three months after diagnosis and stopping nine months later was in the 'exposed' group from 3 to 9 months plus 60 days, and 'non-exposed' thereafter. The entry date was the first gabapentinoid prescription, and the event date was the first overdose following the gabapentinoid prescriptions. Patients without overdose incidents were censored at the earliest of the following: death, leaving the practice, transfer-out, or study end date.

Results were reported as HR and 95% CI for overdose rates during exposed versus non-exposed periods. The reference group was the non-exposed periods. Findings were presented as both unadjusted and adjusted HRs, accounting for potential confounders.

Age was analysed as both a continuous and categorical variable. For categorical analysis, age at treatment start was divided into six ranges (18-30, 31-40, 41-50, 51-60, 61-70, and >70 years) to stratify risk across different age groups.

The strategy used for identifying other confounding variables was:

Step 1: Fit a model with the exposures of interest.

Step 2: Conduct a univariate analysis by sequentially adding each potential confounder, along with a priori confounders, to the model from Step 1. This method allows for an understanding of the individual effect of each variable on the response variable and mitigates the risks of model instability and overfitting, particularly in cases of limited sample sizes (Kutner et al., 2005). A potential confounder was included in the fully adjusted model in Step 3 if it altered the effect of the exposure by 10% or more.

Step 3: Fit the fully adjusted multivariable Cox proportional hazards regression model using the variables identified as potential confounders in Step 2.

Before conducting the primary survival analysis, the survivor function was evaluated graphically and tested for equality. Schoenfeld residuals validated the proportional hazards assumption.

2.2.3.10.1 Graphical assessment of survivor function

A Kaplan-Meier (KM) curve was generated to estimate the occurrence of an overdose according to exposed and non-exposed periods for each gabapentinoid group.

2.2.3.10.2 Statistical assessment of the equality of survivor function

The log-rank test checked for significant differences in overdose incidence between exposed and non-exposed periods. The null hypothesis stated no difference in the survivor function between periods with and without gabapentinoid use.

2.2.3.10.3 Proportionality of hazards assumption tests

KM and Schoenfeld's residuals were used to evaluate the proportionality of the hazards (PH) assumption, with a significant p-value indicating a violation of the PH assumption.

2.2.4 Study 4: the association between gabapentinoid use and all-cause mortality

2.2.4.1 Study design

This study employs the same design as Study 3 (Section 2.2.3.1) to evaluate the association between gabapentinoid use and all-cause mortality in patients with a chronic pain diagnosis. However, in this study, CPRD data was linked to ONS data. The rationale for selecting this study design is discussed in Study 3 (Section 2.2.3.1.1) of this chapter.

2.2.4.2 Data source

This study used primary care records from the CPRD, linked to mortality data from ONS death certificates. A brief overview of the CPRD is presented previously in Section 2.2.1.1. The ONS is the UK's authority for official statistics, collecting and disseminating economic, demographic, and social data at national, regional, and local levels (GOV.UK, 2022). It conducts the decennial census in England and Wales and publishes mortality statistics under the National Statistics logo, adhering to the Code of Practice for Statistics to ensure integrity and independence (ONS, 2022). England and Wales have maintained comprehensive death records since 1837, with each death documented by a Medical Certificate of Cause of Death (MCCD) issued by a doctor (ONS, 2022).

The ONS provides death registration data, including causes and official dates of death, which must be recorded on the Registration Online (RON) system within five days, extendable in exceptional cases (ONS, 2022). Accurate recording in line with ICD-10 is essential (Delmestri and Prieto-Alhambra, 2020). Validation tests on RON data ensure accuracy, with the ONS conducting regular diagnostic tests to identify

discrepancies. Independent Scientific Advisory Committee (ISAC) authorisation is required to access ONS death registration data (Delmestri and Prieto-Alhambra, 2020). The latest release covers records from January 2, 1998, to June 22, 2020 (CPRD, 2021a).

2.2.4.2.1 Rationale for selecting linked CPRD to ONS data for all-cause mortality

Mortality is a primary measure in EHR-based research, extensively studied using the CPRD GOLD database (Alatorre et al., 2018; Lane et al., 2017; Parisi et al., 2017; Stewart et al., 2017; Strongman et al., 2017). Accurate death date documentation is crucial for mortality analysis and end-of-life research. However, the precision of death date entries in CPRD GOLD has been questioned (Harshfield et al., 2020). In England and Wales, GPs may lack information on patients they did not certify. Variations in primary care software and data transitions can impact data quality. Linking CPRD GOLD with the ONS death register is recommended to reduce data transmission delays, with CPRD providing access to linked data for consenting practices (ONS, 2019; CPRD, 2021a).

ONS-linked death data is more reliable than HES-linked data, as over 50% of UK deaths occur outside hospitals, such as in private homes, which HES does not capture (ONS, 2021a). While CPRD GOLD may lack cause of death documentation, its death date accuracy is reliable (Gallagher et al., 2019). ONS data, based on legally mandated medical certificates, is authoritative for mortality records. When linked to CPRD GOLD, these records provide insights into causes of death not available through primary care (Glover et al., 2017; Ratib et al., 2015; Wing et al., 2016). The CPRD-ONS linkage is widely recommended for accurately determining death dates and causes (Delmestri and Prieto-Alhambra, 2020; Gallagher et al., 2019; Tammes et

al., 2018). In conclusion, record linking between CPRD and ONS databases is crucial for accurately estimating mortality rates and causes of death.

2.2.4.3 Study population

The patients included in this study are the same as those identified in the previous study (Study 3; Section 2.2.3.3). However, they had records in the CPRD linked to ONS data. The procedure to identify patients with chronic pain using gabapentinoids and to extract relevant data was explained in Section 2.2.1.3.3 of this chapter.

2.2.4.4 Follow up period

A patient's entry date was determined by the date of the first recorded gabapentinoid prescription in the CPRD. Subsequently, they were followed up until the date of death as identified by the CPRD or ONS, transfer out, or the end of the study period (31st July 2020), whichever occurred first. The starting period of the data sources (CPRD and ONS), gabapentinoid exposure, and follow-up period are summarised in Figure 2-9.

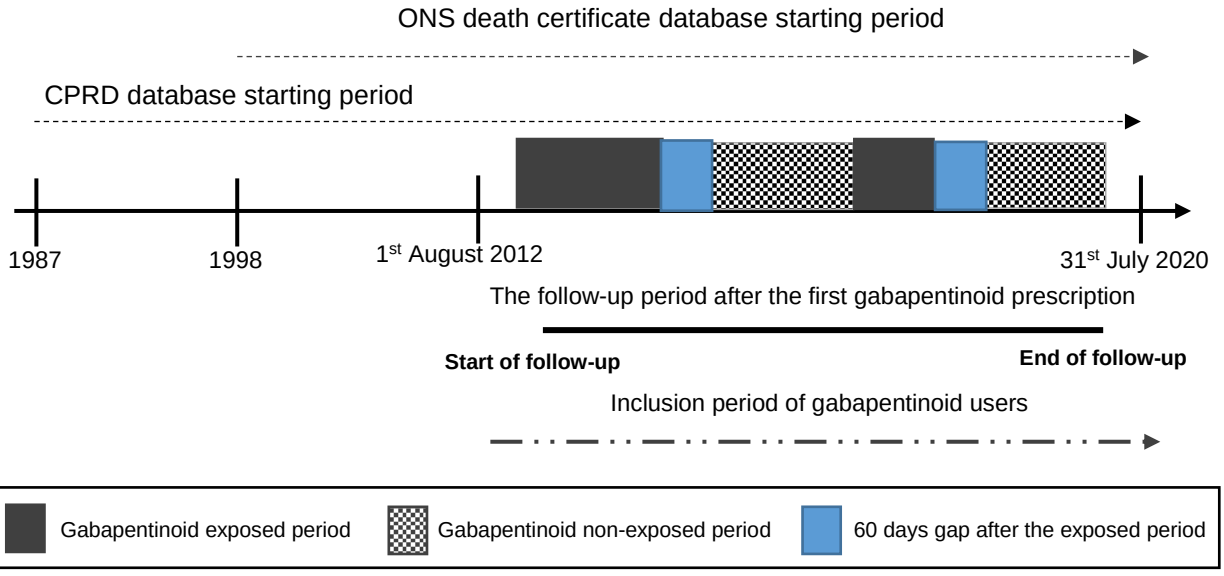


Figure 2-9: Time Period of Data Source, Gabapentinoid Exposure, and Follow-Up this figure illustrates the time periods of data sources used in the study (CPRD linked to ONS), including the exposed and non-exposed periods of gabapentinoid use, and the follow-up period of the study. A 60-day gap was added after the exposed period to account for any delays in initiating a prescription, accumulating tablets, or any outcomes that occurred within withdrawal periods.

2.2.4.5 Exposure

The primary exposure of interest in this study was detailed in the previous study (Study 3; Section 2.2.3.5), which also summarised the exposure groups and exposure periods.

A sensitivity analysis assessed whether changes in the duration of the exposed periods' end (comparing 30 and 90 days to the standard 60 days) influenced the association between gabapentinoid use and all-cause death.

2.2.4.6 Time-varying (analysis time definition)

The analysis time definition was similar to that in Study 3 of this chapter, with details summarised in Study 3, Section 2.2.3.6.

2.2.4.7 Outcome measures

2.2.4.7.1 Number and proportion of death events in CPRD, ONS, or both

Patients were grouped by the number and proportion of death dates recorded in the CPRD, ONS, or both. Table 2-6 presents the operational definitions and corresponding patient groups. The data extraction process is shown in Figure 2-10. If death dates were recorded in both databases, the ONS date was used in the analysis.

Table 2-6: Operational and Practical Definitions of Patient Groups According to Death Records in CPRD, ONS, or Both Databases

Patient group	Operational definition	A practical definition of the patient group
Group 1 (CPRD only)	Patients who had a death recorded only in the CPRD (no death recorded in ONS data).	Those who had a death record in primary care only
Group 2 (ONS only)	Patients who had a record of death recorded only in ONS death	Those who had a death record in the ONS death registration only

Patient group	Operational definition	A practical definition of the patient group
	registration data (no death recorded in the CPRD).	
Group 3 (Both)	Patients with records of death recorded in both the CPRD and ONS databases.	Those who had death dates recorded in both PC and ONS records
Group 4 (Censored observation)	Patients who did not have a death record in either the CPRD or ONS data (indicating the patient is alive).	Those who did not die during the study according to both databases: no GP record or ONS record of death.

CPRD: Clinical Practice Research Datalink; GP: General Practice; ONS: Office for National Statistics; PC: primary care

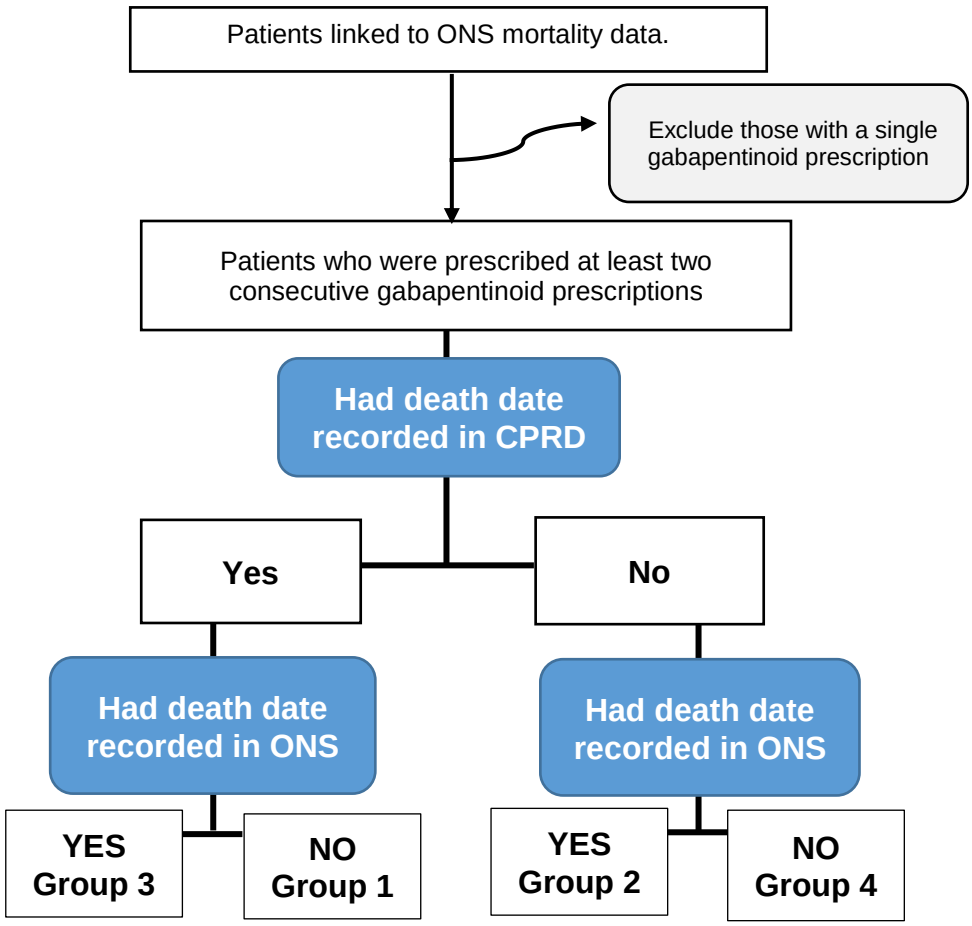


Figure 2-10: Flow Diagram Outlining the Process of Patient Group Identification According to the Existence of Death Date

2.2.4.7.2 Comparison of dates of death recording in both databases (CPRD – ONS)

For Group 3 patients with death records in both databases, the date of death was identified, and the gap between the two dates was calculated. This gap was used to classify patients, as shown in Table 2-7. These definitions were adapted from Gribbin's (2013) work on falls in primary care.

Table 2-7: Time Gap between Death Recording Dates in CPRD and ONS Datasets: Category and Definition

Time Gap Category	Definition
No gap	The death date in the CPRD and ONS was recorded on the same date.
Very short gap	If the gap between the death dates recorded in the CPRD and ONS was less than or equal to 2 days
Short gap	If the gap between the death dates recorded in the CPRD and ONS was more than 2 days but less than or equal to 7 days.
Intermediate gap	If the gap between the death dates recorded in the CPRD and ONS was more than 7 days but less than or equal to 14 days.
Long gap	If the gap between the death dates recorded in the CPRD and ONS was more than 14 days but less than or equal to 30 days.
Prolong gap 1	If the gap between the death dates recorded in the CPRD and ONS was more than 30 days but less than or equal to 60 days.
Prolong gap 2	If the gap between the death dates recorded in the CPRD and ONS was more than 60 days but less than or equal to 90 days.
Prolong gap 3	If the gap between the death dates recorded in the CPRD and ONS was more than 90 days.

CPRD: Clinical Practice Research Datalink; ONS: Office for National Statistics

2.2.4.7.3 All-cause mortality and cause of death

The primary outcome was all-cause mortality, identified by the recorded death date during the study. The definition, adapted from published pharmacoepidemiology studies and ICD-10 mortality codes, is detailed in the ONS death guide (Molero et al.,

2019; ONS, 2021a; WHO, 2016). Appendix XI lists the mortality ICD-10 codes. Deaths from the ONS were categorised into all-cause deaths and DRDs, while those from the CPRD alone were classified as unknown cause. Table 2-8 presents the clinical and operational definitions of the three death categories.

Table 2-8: Clinical and Operational Definition of Death Categories

Death category	Clinical definition	Data source	Operational definition
Unknown cause of death	All deaths occurred without a known cause of death	CPRD	The record of the death date or transfer out of the practice due to death in the CPRD database.
All-cause deaths	All deaths where the cause of death recorded on the death certificate was any cause not related to drugs (non-drug-related deaths).	ONS	One of the ICD-10 diagnosis codes related to non-drug causes of death in the ONS death registries.
Drug-related death	Deaths that occurred when the cause of death recorded on the death certificate was any drug poisoning.	ONS	One of the ICD-10 diagnosis codes related to drug or drug poisoning as a cause of death in the ONS death registries.

CPRD: Clinical Practice Research Datalink; ICD-10: International Classification of Diseases, Tenth Revisions; ONS: Office for National Statistics

2.2.4.8 Potential confounding variables

The potential baseline variables were measured for each patient during the year before the start of their gabapentinoid prescription in the study period. These confounders were the same as those described in Study 3 (see Study 3, Section 2.2.3.8 for details).

2.2.4.9 Data management

Before analysis, data checks ensured correctness, completeness, and validity of the CPRD files. Detailed data management procedures of CPRD files are in Study 1,

Section 2.2.1.6. ONS data were imported in .txt format into STATA 17.0 for analysis. Inconsistencies and missing dates were checked and eliminated.

2.2.4.10 Statistical analysis

The proportion of patients with a death date recorded in either the CPRD or ONS was reported for each database during the follow-up period. If recorded in both, the ONS date was used in the analysis.

To estimate the association between gabapentinoid exposure (pregabalin and gabapentin) and mortality risk, a Cox proportional HR was used, treating gabapentinoid exposure as time-varying. This accounted for immortal time bias, changing treatment periods, and switches between treatment and no treatment (Agarwal et al., 2018). The analysis included the death date after starting gabapentinoids. Patients who did not die were censored at the earliest of: leaving the practice, transfer-out date, or study end date (31st July 2020).

The study compared current gabapentinoid use (gabapentin, pregabalin, and both) with no current use, determining the HR and 95% CI for each exposure. The HR indicates the ratio of death rates during exposed vs. non-exposed periods for each participant. The reference group was the non-exposed periods. Results were reported as unadjusted and adjusted HR (95% CI) after accounting for potential confounders.

The analysis time was divided into two periods: 0 to 0.5 years and 0.5 to 8 years for the gabapentin group, and 0 to 0.4 years and 0.4 to 8 years for the pregabalin group. This division was necessary due to violated proportional hazards assumptions, indicated by crossing log-log curves (Thomas and Reyes, 2014; Bouliotis and Billingham, 2011). Since the first period is less than six months, the primary study

focused on the second period to examine the association between gabapentinoid use and all-cause mortality.

The age at which patients started treatment was analysed both as a continuous and categorical variable, categorised into six groups: 18–30, 31–40, 41–50, 51–60, 61–70, and over 70 years, to identify high-risk groups for death.

The strategies for identifying other potential confounding variables are described in detail in Study 3, Section 2.2.3.10.

2.2.4.10.1 Graphical assessment of survivor function

The study's graphical assessment of survivor function was analysed using the Kaplan-Meier curve to estimate the death rate based on the exposure and non-exposed periods for each group.

2.2.4.10.2 Statistical assessment of the equality of survivor function

The log-rank test was then performed to analyse the effects of different exposure groups on the incidence of death between the varying periods (exposed and non-exposed). The null hypothesis posits that specific exposures do not affect the survivor function.

2.2.4.10.3 Proportionality of hazards assumption tests

The Schoenfeld residuals test was subsequently used to evaluate the proportional hazards assumption. This test determined whether the hypothesis was violated.

2.3 Ethical approval

Access to patient data recorded in the CPRD requires approval from the CPRD ISAC (Studies 1 and 2). Similarly, accessing ONS death registration data (Study 4) and HES APC data (Study 3) also necessitates ISAC approval. This research study has secured

approval from ISAC, with the protocol number 20_000149. The ISAC protocol form is provided in Appendix I.

Chapter 3 Trends and patterns of gabapentinoid prescribing in patients with chronic non-cancer pain

3.1 Introduction

Existing studies on gabapentinoid prescribing in chronic pain patients are limited and lack detail on the annual prevalence, incidence, PDD, and days of supply. This study aims to address this research gap by examining gabapentinoid prescribing trends and dosing patterns in CNCP patients over 16 years, contributing to a better understanding of primary care prescription trends over time. Moreover, it determines the proportion of users prescribed gabapentinoids for neuropathic versus non-neuropathic pain. The findings will inform future prescribing practices and guidelines, providing a clearer understanding of the utilisation of these medications in clinical practice.

3.2 Aim and objectives

The aim of the study was to describe the trend in prescribing and dosing patterns of gabapentinoids (gabapentin and pregabalin) in primary care patients diagnosed with chronic pain over a 16-year period (from 1st January 2005 to 31st December 2020). The specific study objectives were:

(1) To describe the baseline demographics of the study cohort;

(2) To quantify the use of each pregabalin and gabapentin through the following repeat annual measures:

   a) Number of prescriptions

   b) Number of prescribed daily doses

   c) Number of days of drug supply

(3) To estimate the annual prevalence and incidence of gabapentinoid users amongst patients with chronic pain (i.e., the number of existing and new users of pregabalin and gabapentin among patients with chronic pain).

For detailed information about the method, please refer to Chapter 2, Section 2.2.1.

3.3 Results

3.3.1 Patients' characteristics

In total, a cohort of 415,179 adult patients, who were 18 years of age or older at the time of their initial prescription for a gabapentinoid, were identified as having chronic pain from 2005 to 2020. These patients were subsequently prescribed either pregabalin and/or gabapentin throughout the duration of the study. Among the total population, 101,394 (24.4%) used pregabalin, and 229,016 (55.2%) used gabapentin. In addition, 84,769 individuals (20.4%) used both, switching from pregabalin to gabapentin or vice versa, as shown in Table 3-1.

Table 3-1: Demographic Characteristics of Gabapentinoid Users (N=415,179)

Characteristics		Gabapentin* n (%)	Pregabalin* n (%)	Both users* n (%)
Number of patients		229,016 (55.2)	101,394 (24.4)	84,769 (20.4)
Gender	**Male**	87,639 (38.3)	38,327 (37.8)	29,168 (34.4)
	Female	141,375 (61.7)	63,065 (62.2)	55,599 (65.6)
Age[a] at baseline (years)	**Median (IQR)**	57 (45 -70)	55 (45 -70)	56 (45-69)
	18≤age≥25	6,175 (2.7)	3,542 (3.5)	6,860 (8.1)
	26≤age≥35	19,178 (8.4)	10,192 (10.1)	14,075 (16.6)
	36≤age≥45	33,422 (14.6)	16,786 (16.6)	19,021 (22.4)
	46≤age≥55	46,386 (20.3)	20,386 (20.1)	17,040 (20.1)
	56≤age≥65	46,085 (20.1)	18,471 (18.2)	14,596 (17.2)
	66≤age≥75	41,252 (18)	16,286 (16.1)	11,367 (13.4)
	76≥age	36,518 (15.9)	15,731 (15.5)	1,810 (2.1)

IQR: interquartile range; n: number of sample
*2 patients were with unspecified gender for pregabalin, gabapentin and both
[a] Calculated at start of gabapentinoid treatment

3.3.2 The number of gabapentinoid prescriptions

A total of 8,877,895 gabapentinoid prescriptions were issued from January 2005 to December 2020. Out of these, 3,885,872 (43.8%) prescriptions were for pregabalin

and 4,991,023 (56.2%) for gabapentin. The annual number of gabapentinoid prescriptions issued for patients with chronic pain over the study period increased from 142,276 to 688,533 prescriptions. The annual number of pregabalin prescriptions for a chronic pain diagnosis increased 13-fold (from 26,540 in 2005 to 356,336 in 2020). Between 2005 and 2020, the annual number of gabapentin prescriptions increased by 2.9-fold (from 115,736 in 2005 to 331,197 in 2020).

The highest annual number of gabapentinoid prescriptions per 1000 CPRD registrants was attained in 2018, reaching 317.6. However, this figure declined to 216 per 1000 in 2020. There was a notable increase in the annual number of prescriptions per 1000 CPRD registrants within the pregabalin group, rising from 5.19 to 111.9 prescriptions per 1000 CPRD registrants between the years 2005 and 2020. Throughout the designated research period, there was a notable increase in the annual number of gabapentin prescriptions per 1000 registrants. Specifically, there was a 4.6-fold rise, with the number of gabapentin prescriptions per 1000 registrants escalating from 22.6 in 2005 to 104 in 2020. In 2018, pregabalin and gabapentin exhibited the highest annual prescription rates per 1000 registered patients, with 151 and 165 prescriptions per 1000 registrants, respectively (Figure 3-1).

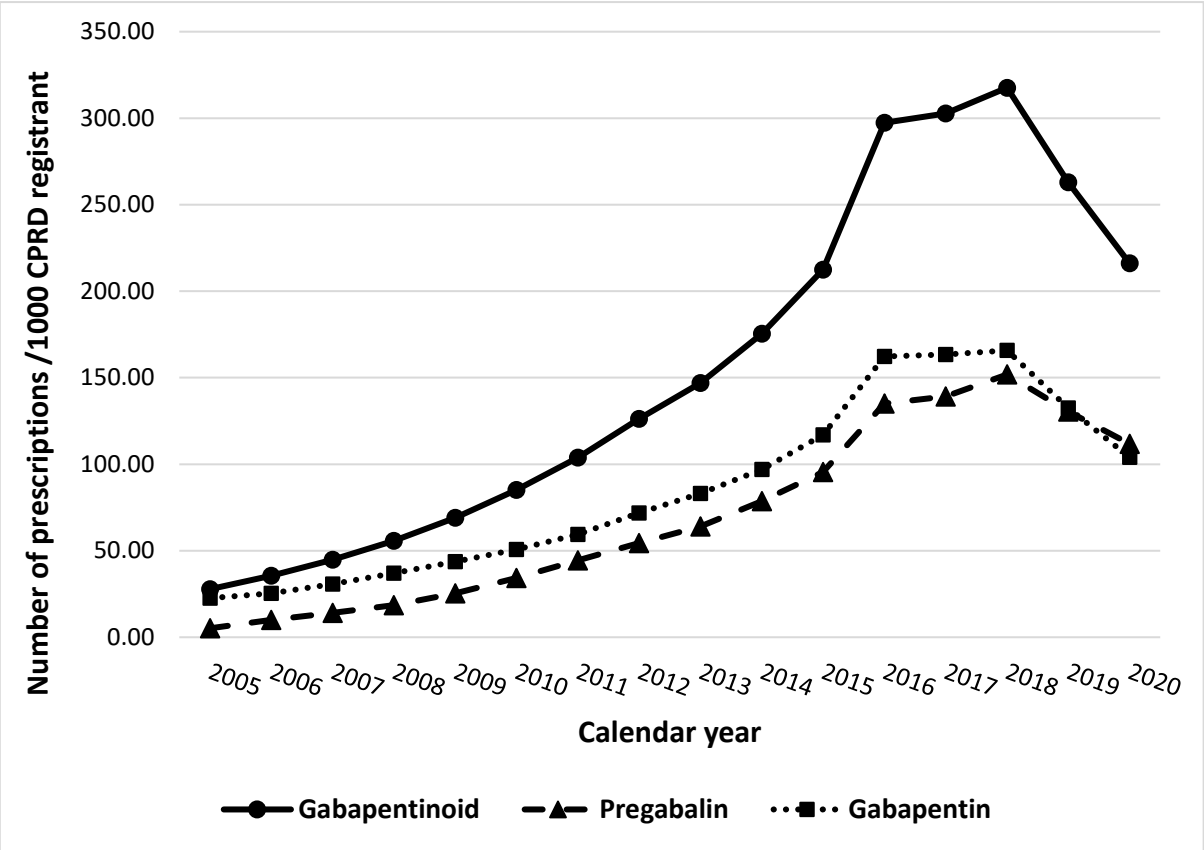


Figure 3-1: Annual Number of Gabapentinoid Prescriptions per 1000 CPRD Registrants from 2005 to 2020

3.3.3 The annual prevalence of pregabalin and gabapentin users / 10,000 CPRD registrants

In accordance with the previous result in section 3.4.2 of the yearly patterns of gabapentinoid prescriptions per 1000 CPRD registrants, there was a general rise in the prevalence of pregabalin and gabapentin users (measured as the annual number of patients per 10,000 CPRD registrants) throughout the follow-up period from 2005 to 2016. The data indicate a consistent upward trend in the number of patients prescribed pregabalin from 2005 to 2016. Subsequently, there was a period of relative stability between 2016 and 2018, followed by a slight decline in 2020. Specifically, the number of patients per 10,000 registrants increased from 12.8 in 2005 to 108.9 in 2020. Between 2005 and 2016, there was a noticeable increase in the number of

patients prescribed gabapentin, which then slightly decreased starting from 2017 to 2020. Specifically, the gabapentin users rate per 10,000 registrants increased from 38.8 in 2005 to 245 in 2016, and subsequently decreased to 125 per 10,000 registrants in 2020 (Figure 3-2).

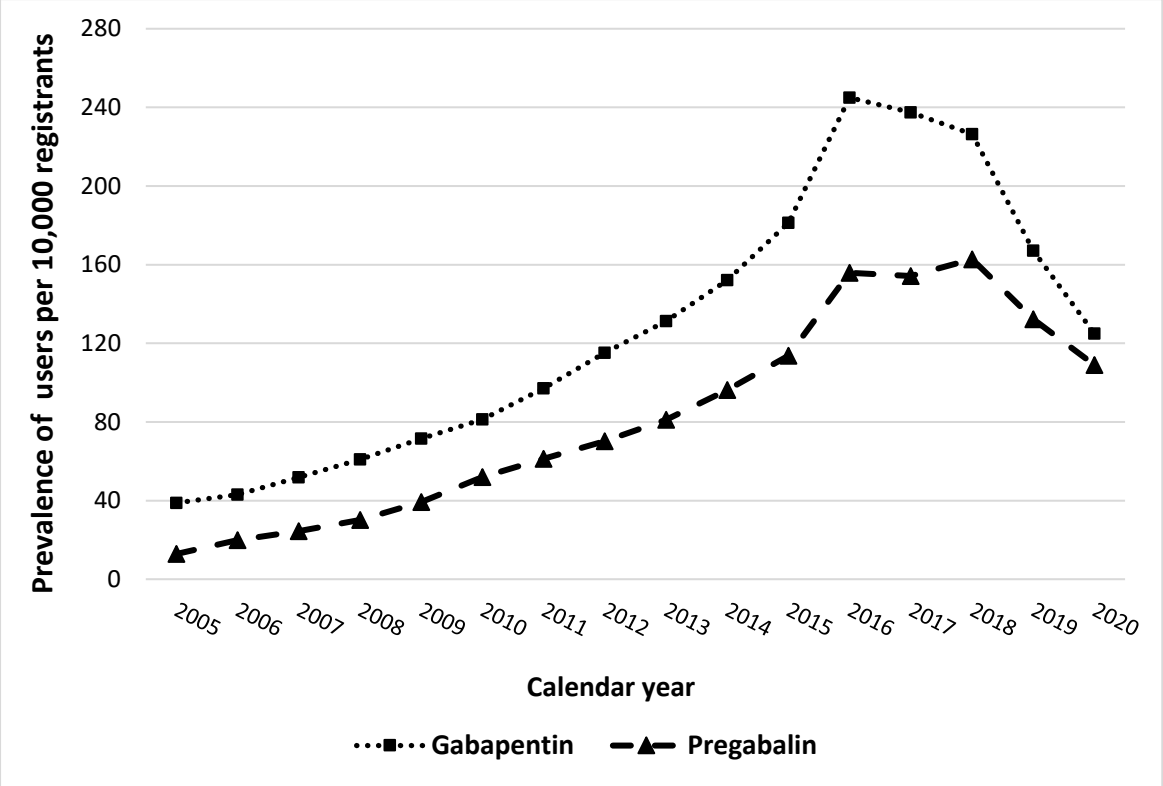


Figure 3-2: Annual Prevalence of Gabapentinoid Users per 10,000 Registrants between 2005 and 2020

3.3.4 The annual incidence of pregabalin and gabapentin users /10,000 CPRD registrants

The annual incidence of new gabapentinoid users has exhibited a consistent upward trend throughout the study period, spanning from 2005 to 2017. There was a consistent and gradual rise in the number of patients receiving new prescriptions for gabapentin from 13.8 to 69.4 per 10,000 registrants between the years 2005 and 2017. However, this figure declined to 49.7 per 10,000 registrants in the year 2020. The

annual incidence of individuals using pregabalin witnessed a notable rise, going from 8 per 10,000 registrants in 2005 to 41.8 per 10,000 registrants in 2017. However, it subsequently experienced a gradual decline, reaching 38.5 per 10,000 registrants in 2020 (Figure 3-3).

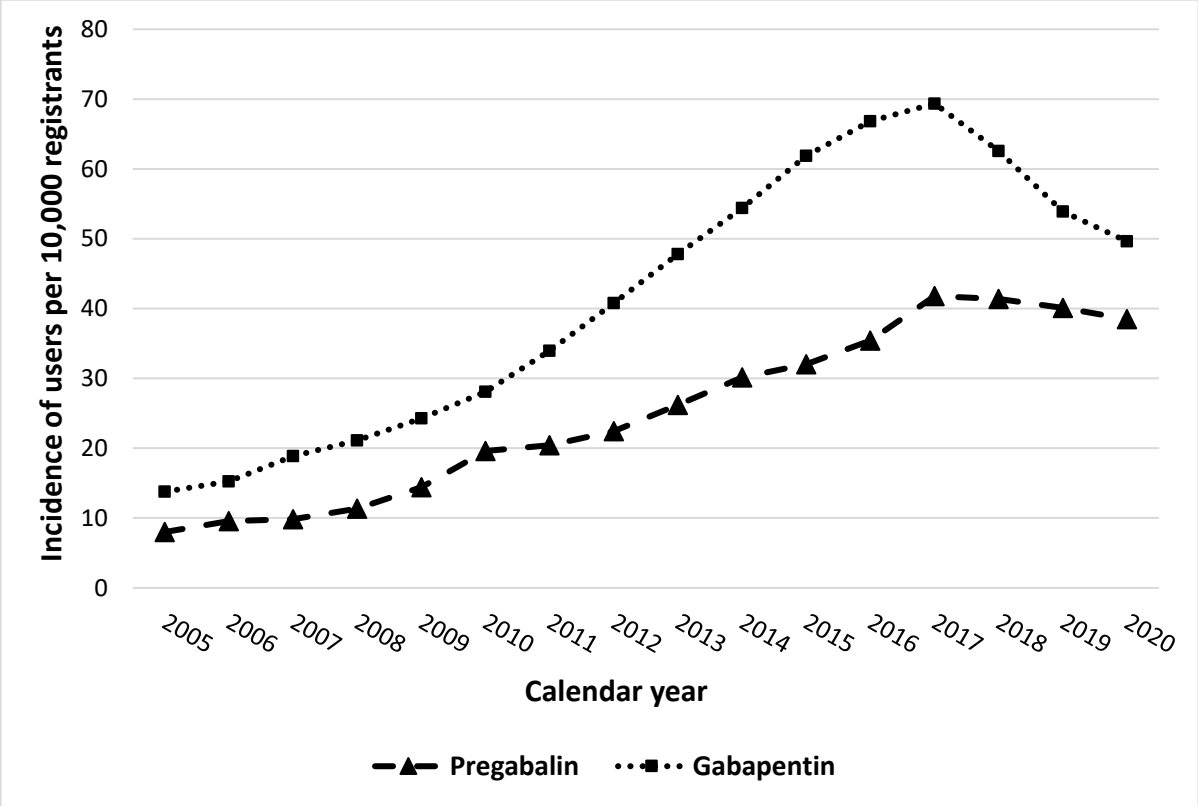


Figure 3-3: Annual Incidence of Gabapentinoid Users per 10,000 Registrants between 2005 and 2020

3.3.5 Prescribed daily dose of pregabalin and gabapentin among chronic pain patients

During the period of analysis from 2005 to 2020, a consistent upward trend was observed in the annual average PDD for individuals utilising pregabalin and gabapentin. It is important to underline that the majority of PDD values fell within the approved normal range for both medications. The average PDD of pregabalin demonstrated an increasing pattern, escalating from 264 mg per patient per day in 2005 to a peak of 653 mg per patient per day in 2020. As reflected in Table 3-2, starting

in 2018, the average PDD of pregabalin has consistently been higher than the recommended maximum daily dose of pregabalin (>600 mg/d). The average daily prescribed dose of gabapentin per user showed a gradual upward trend over time. The average daily dosage increased from 1002.8 mg in 2005 to 1210 mg in 2020, as illustrated in Table 3-2. However, the administered doses of gabapentin fell within the standard dosage range and did not exceed the maximum daily dose prescribed (3600 mg/d).

Table 3-2: The Annual Average Prescribed Daily Dose per Users per Day

	Pregabalin		Gabapentin	
Calendar Year	**Number of patients**	**PDD (mg/d)**	**Number of patients**	**PDD (mg/d)**
2005	5,901	264.0	16,981	1002.8
2006	7,135	350.7	19,494	987.8
2007	7,568	415.4	23,840	966.2
2008	8,841	441.2	27,931	965.4
2009	11,421	437.3	32,826	976.1
2010	14,958	440.5	37,363	982.6
2011	15,431	504.3	43,761	983.9
2012	16,264	550.8	50,967	988.0
2013	17,881	574.5	57,198	995.5
2014	18,704	541.1	60,672	994.7
2015	16,803	512.6	60,284	1008.1
2016	14,763	540.2	53,883	1016.4
2017	13,084	577.7	48,654	1028.5
2018	13,193	605.1	43,023	1033.5
2019	13,182	634.2	40,401	1122.0
2020	13,179	653.0	39,787	1210.2

PDD: Prescribed Daily Dose

3.3.6 Chronic pain indications for pregabalin and gabapentin prescriptions

Compared to the licensed indication (neuropathic pain), the most commonly recorded chronic pain diagnoses were unlicensed (off-label) pain indications, specifically back pain and musculoskeletal joint pain. Back pain and musculoskeletal joint pain were the most common unlicensed pain indications recorded for 84,337 patients (36.8%) and 56,458 patients (24.7%), respectively, during the year prior or 180 days after the first gabapentin prescription. Only 21.7% of the patients initiated on gabapentin had a neuropathic pain diagnosis during the same period prior to or after the first gabapentin prescription. Furthermore, the most common diagnosis associated with the initial prescription of pregabalin for CNCP was for an unlicensed indication, specifically back pain, with a total of 37,378 patients, accounting for 36.9% of the cases (Table 3-3).

Regarding the licensed indication, a total of 18,995 (18.7%) individuals had neuropathic pain attributed to the initial prescription of pregabalin. In both groups, where patients were switched between the two medications, it was observed that over 60% of the initial prescriptions were attributed to unlicensed indications, as shown in Table 3-3.

Table 3-3: The Number of Patients Prescribed Their First Gabapentinoid Attributed to the Initial Chronic Pain Diagnosis (n=415,179)

Pain type	Gabapentin n=229,016		Pregabalin n=101,394		Both n=84,769	
	Freq.	Percent	Freq.	Percent	Freq.	Percent
Licensed indication						
Neuropathic pain	49,651	21.7	18,995	18.7	20,230	23.86
Unlicensed indications						
Back pain	84,337	36.8	37,378	36.9	30,723	36.24
Fibromyalgia pain	4,845	2.1	3,796	3.7	3,840	4.53
Headache and migraine	32,863	14.4	16,048	15.8	11,740	13.85
Musculoskeletal pain	56,458	24.7	24,620	24.3	17,643	20.81
Other						
Other chronic pain	862	0.4	557	0.6	593	0.7

Freq.: frequency
*Patients who switched between the two medications

3.3.7 Days' supply of pregabalin and gabapentin among chronic pain patients

The annual number of days' supply of gabapentinoids gradually increased from 2005 to 2020. The days' supply for pregabalin increased from 124.7 days in 2005 to 336 days in 2020, representing a 169.4% increase. Similarly, the days' supply for gabapentin increased from 228.3 days in 2005 to 301 days in 2020, indicating a 31.8% increase (Figure 3-4).

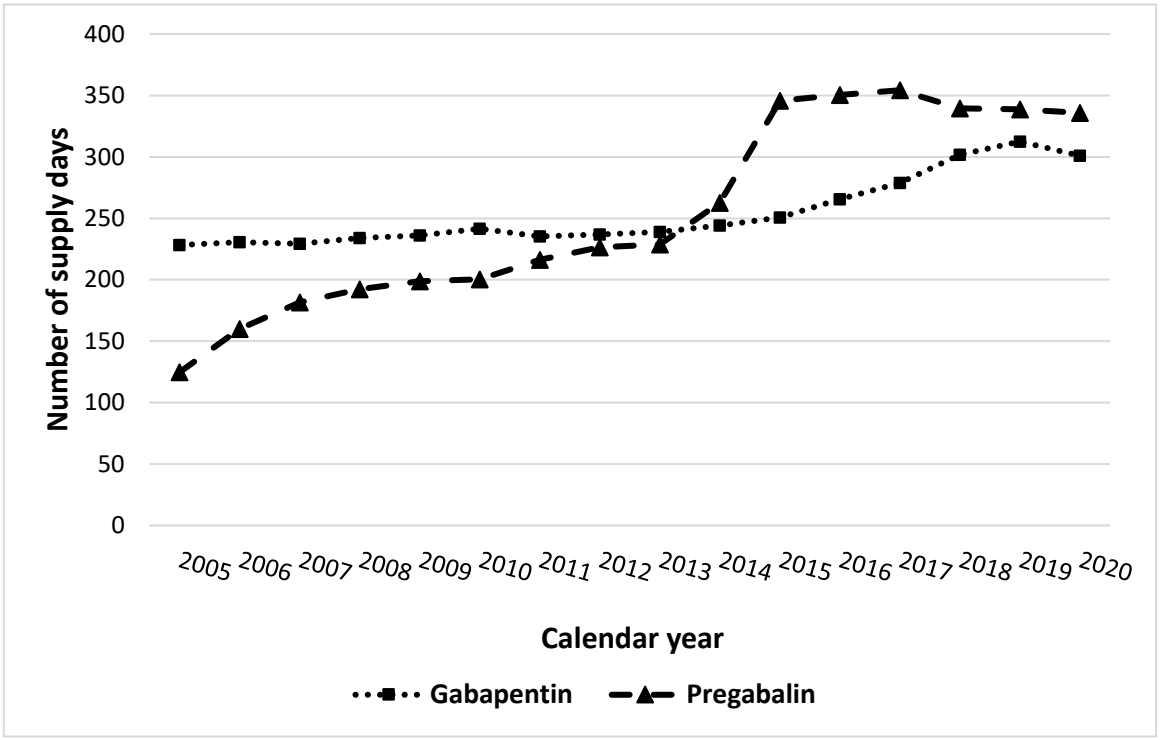


Figure 3-4: Annual supply days for pregabalin and gabapentin users from 2005-2020

3.4 Discussion

3.4.1 Main findings

This cross-sectional study represents the first investigation describing the trends in gabapentinoid prescribing within the chronic pain population in the United Kingdom. It has identified a significant overall upward trend in the prescription rates of gabapentinoid medications (gabapentin and pregabalin) for patients suffering from chronic pain in the primary care setting from 2005 to 2020. The annual number of gabapentinoid prescriptions per 1000 registrants experienced a 7.8-fold increase from 2005 to 2020. This study presents findings that indicate a notable rise in the prescription rates of GBP and PGB from 2005 to 2018, followed by a decline in prescription rates over the last two years (2019–2020). However, by the end of the study, the prescription rate in 2020 remained high compared to the rate in 2005. Specifically, gabapentin saw a 4.6-fold increase in prescription rate over this time period, whereas greater increases in the pregabalin prescription rate were demonstrated with a 21-fold increase.

Throughout the study period from 2005 to 2017, there was a general rise in the yearly incidence of people using pregabalin and gabapentin for chronic pain. The annual incidence rate of individuals using gabapentin reached its highest point in 2017, followed by a marked decline in the number of new gabapentin users in the years leading up to 2018 through 2020. Likewise, the incidence rate among new pregabalin users showed an increasing trend, peaking in 2017, and then experienced a consistent decline in the subsequent years from 2018 to 2020. The annual incidence of pregabalin and gabapentin users per 10,000 registrants increased by 4.8-fold and 3.6-fold, respectively, during the study period (2005-2020).

The decline in the annual incidence rate of gabapentin and pregabalin users may be attributed to various factors, such as the release of advice recommendations on pregabalin and gabapentin by the ACMD in 2016, instances of mortality, or the transfer out of gabapentin or pregabalin users from the CPRD database. The ACMD, which advises the government in the UK, provided advice on these drugs following observed patterns of misuse and associated harm. This advice includes several key points, including the recommendation to place these drugs under more stringent control due to their abuse potential. Moreover, it advises stricter guidelines for prescribing these medications to reduce the risk of misuse. This might include limited quantities per prescription or closer monitoring of patients, suggesting increased education for healthcare professionals and patients regarding the risks of dependence and the potential for misuse. In addition, it recommends the development of specific treatment and support strategies for individuals who misuse these drugs or have developed a dependency (Bradley, 2016).

The study period from 2005 to 2020 revealed an increasing trend in the annual prevalence of pregabalin and gabapentin users. The study showed a higher number of gabapentin users compared to pregabalin users. One possible explanation is that gabapentin received approval as an analgesic medication before pregabalin. However, the annual prevalence rate of gabapentin users per 10,000 registrants increased by 3.2-fold, while a significant rise of 8.5-fold was observed in the annual prevalence rate of pregabalin users between 2005 and 2020. This surge in gabapentinoid users might be linked to the opioid crisis. Increasing awareness of the harmful effects of opioids and the ongoing quest for long-term management and safer alternatives for pain management may explain the substantial rise in prescriptions for gabapentinoids (Shipton et al., 2018). Another reason might be linked to the

pharmaceutical companies actively marketing these drugs for various indications, which can influence prescribing habits (Goodman and Brett, 2019a).

The increase in the prevalence rate of pregabalin users by more than eightfold compared to gabapentin might be linked to the following factors: differences in pharmacokinetics, dosing convenience, therapeutic onset, and the range of approved indications. Pregabalin is absorbed more quickly and efficiently in the digestive system compared to gabapentin. It also has a more predictable absorption rate and bioavailability (Bockbrader et al., 2010). Pregabalin often requires less frequent dosing than gabapentin. Pregabalin can be taken once or twice a day, whereas gabapentin may need to be taken three times a day for effective symptom control. This can make pregabalin a more convenient option for patients (Medicines Complete, 2023a, 2023b). Some patients and clinicians report that pregabalin may have a quicker onset of action in relieving symptoms compared to gabapentin (Frampton and Foster, 2005). This can be particularly beneficial for patients seeking more immediate relief from pain. Pregabalin might have more approved indications than gabapentin, making it a more versatile option for different conditions (NHS, 2021b, 2022a).

Over 60% of initial gabapentinoid prescriptions were for unlicensed indications, predominantly chronic back pain, while nearly 20% were for licensed indications. The increase in gabapentinoid (gabapentin and pregabalin) prescriptions for unlicensed pain indications can be attributed to several factors, such as physician experience, limitations of current analgesics, and pharmaceutical marketing. Despite limited evidence supporting unlicensed use for pain, clinicians may rely on personal experience or the reported success of their peers in managing certain pain conditions. The limitations of current analgesics due to unresponsiveness or experiencing severe side effects (SEs) have led doctors to explore alternatives like gabapentinoids (Payne,

2000; Morrison et al., 2017). For instance, while NSAIDs are useful for managing nociceptive pain such as osteoarthritis or back pain, there are concerns about potential medical complications and adverse effects. These side effects include potential harm to the digestive system associated with both acute and chronic use, blood toxicity during acute use, and kidney damage with prolonged use (Payne, 2000). The pharmaceutical industry's promotion of gabapentinoids based on low-quality and industry-funded studies (Landefeld and Steinman, 2009; Vedula et al., 2009) has influenced this shift. However, cautious use of gabapentinoids is advised due to the risks of misuse and dependence.

During the study period, there has been a marked increase in prescription duration: 31.8% for gabapentin and 169.4% for pregabalin. Moreover, there was a consistent rise in the average prescribed daily dose for both gabapentinoids. There was a 147.3% rise in the prescribed daily dose for pregabalin and a 20.6% increase for gabapentin during the study period. Nevertheless, the observed escalation was within the approved dosage range for pregabalin (150 mg/d to 600 mg/d) and gabapentin (300 mg/d to 3600 mg/d). This observation could potentially be attributed to physicians increasing the dosage to a higher level per the therapeutic objective of pain management and considering the patient's ability to tolerate the medication. However, the recommended daily dosage for gabapentin was not optimal and did not reach 1800 mg per day. This might be due to patient response and tolerability, as well as the prescribing practices of physicians and the concurrent use of other therapies.

3.4.2 Comparison with other studies

The current study observed a general rise in the rate of prescription and number of users of gabapentinoids. The frequency of gabapentinoid prescriptions experienced a

7.8-fold increase between 2005 and 2020. A similar increase in gabapentinoid prescription rates for OA patients was observed within the outcomes derived from a recent, comprehensive population-based study conducted within the United Kingdom (Appleyard et al., 2019). This study reported gabapentinoid prescriptions per 1000 person-years rising from 9.5 to 28.0 between 2005 and 2014 (Appleyard et al., 2019). Leong et al. (2016) reported a substantial increase in gabapentin prescriptions for individuals without a seizure disorder in Canada, increasing by 55 times from 0.2 to 11.1 per 1000 persons between 1998 and 2013. In contrast, patients with epilepsy saw a relatively modest doubling in prescriptions from 21.6 to 41.3 per 1000 persons during the same period.

The finding of this study regarding the increase in the incidence rate of gabapentinoid users aligned with the conclusion of another relevant study that used a primary care database in the UK (Montastruc et al., 2018). Montastruc et al. (2018) revealed a significant rise in the incident rate of GBP and PGB users. This study revealed that the rate of new patients treated with gabapentin rose from 230 to 679 per 100,000 individuals annually, and with pregabalin, it increased from 128 to 379 between 2007 and 2017 (Montastruc et al., 2018). However, gabapentinoid users in this study used gabapentinoids for different general indications (Montastruc et al., 2018). These consistent increases across different studies highlight the necessity for further investigation into the driving factors, which may include shifts in healthcare protocols, patient preferences, or broader public health trends.

This study revealed that over 60% of initial gabapentinoid prescriptions were for non-neuropathic pain. This outcome aligned with the conclusion of a preceding investigation in the United Kingdom, conducted by Montastruc et al. in 2018. This study observed a significant rise in gabapentinoid prescriptions for off-label

indications. The rate of patients receiving gabapentin for off-label uses escalated from 58.7 to 216.0 per 100,000 individuals annually, and for pregabalin, it climbed from 34.7 to 117.8 per 100,000 people per year. In 2017, over half of the gabapentinoid prescriptions were off-label, with the majority for non-neuropathic pain (Montastruc et al., 2018). The off-label indication was defined as non-neuropathic pain, anxiety, substance withdrawal, psychiatric disorders, and restless legs syndrome. Several studies conducted in Canada, Australia, and the US have documented the prevalent off-label prescribing of pregabalin and gabapentin for chronic pain (ranging from 52% to 96%), particularly for back pain (Kwok et al., 2017; Schaffer et al., 2020; Zhou et al., 2019).

A consistent upward trend was observed throughout the study period in the average prescribed daily dose for pregabalin and gabapentin. However, it is important to note that the increase remained within the recommended dose range for gabapentin and pregabalin. Research conducted earlier has established that the responsiveness of patients with chronic pain to pregabalin or gabapentin treatment is intricately linked to the dosage administered. Investigations have consistently shown that higher doses of pregabalin not exceeding the recommended dose (600 mg) yield effective outcomes, specifically those equal to or exceeding 300 mg per day. This conclusion finds solid support in the results of studies conducted by Derry et al. (2019), Arnold et al. (2018), Davies (2018), and Zhang et al. (2015), all of which underscore the therapeutic efficacy of pregabalin at these elevated dosage levels. The cumulative evidence from these independent studies reinforces the significance of dose-dependent responses. It highlights the potential benefits associated with the use of higher doses in managing chronic pain conditions.

The average PDD of gabapentin was found to be suboptimal, whereby most patients were prescribed a dose below 1200 mg per day. The literature has steadily underscored that patients utilising gabapentin for neuropathic and FM pain management have highlighted optimal pain relief when administered at 1800 mg or more daily (North et al., 2015; Cooper et al., 2017; Zhang et al., 2018; Moore et al., 2018). The suboptimal dosage of gabapentin may be attributed to factors such as patient tolerability or the presence of risk factors, such as a diagnosed substance use disorder or concurrent use of other medications, including opioids. This intricate interplay between dosing strategies, patient characteristics, and the nature of the presenting pain conditions underscores the complexity of tailoring treatments to achieve the best possible outcomes.

3.4.3 Strength and limitation

This study has several strengths that warrant attention. A key factor underpinning this research is the use of the comprehensive CPRD GOLD datasets. This large database uniquely facilitates a detailed examination of prescription and dosage patterns for gabapentinoid drugs in the UK. Including a substantial group of primary care patients from various regions of the UK, the dataset enhances the generalisability of the study's findings. Additionally, it is important to consider the duration of the observation period. A 16-year period was allocated to provide an extensive observation window, enabling the tracking of changes in gabapentinoid prescribing for patients with chronic pain over a meaningful clinical and regulatory time frame. This facilitated the acquisition of valuable insights into prescribing practices in primary care settings in the UK. In contrast to previous drug utilisation studies, the current study measured the utilisation of gabapentinoid (pregabalin and gabapentin) medications in clinical practice for a

variety of chronic pain conditions, including neuropathic pain, back pain, fibromyalgia, headache, migraine, and musculoskeletal pain.

To our knowledge, this is the first study to use PDD to estimate the change in gabapentinoid drug utilisation. The use of PDD was preferred over the defined daily dose (DDD) due to various factors. First and foremost, it's important to recognise that the standard DDD is geared towards primary medical use as outlined by the WHO. In the case of gabapentinoids, their primary use is for treating epilepsy. However, it's worth noting that different dosages may be employed for a range of other symptoms or conditions. In this study, the main focus is on exploring the use of gabapentinoids in the context of pain management, despite their different primary indications. Additionally, the objective of the WHO is for the DDD to function as a consistent measure in order to establish a standardised level of drug utilisation rather than reflecting the specific prescribed dosage. However, PDD refers to the typical daily dosage of medication that is prescribed. Dose adjustments for renal or hepatic impairment are not made in DDD. In certain instances during clinical practice, making adjustments for certain patients may be necessary. These adjustments may be particularly important for patient groups, including individuals with conditions requiring dose modification.

Some limitations of the study must also be considered. Firstly, the data provided pertains specifically to primary care and does not include prescriptions for gabapentinoids that specialists in secondary care issue. However, in the United Kingdom, primary care providers are typically still in charge of prescribing any prescriptions that specialists recommend. Although specialists may occasionally initiate the first prescription, general practitioners are frequently in charge of continuing prescriptions. As a result, the reported findings are still expected to accurately

represent the prescribing trends of gabapentinoids within primary care in the UK. Secondly, since the diagnoses in the CPRD database may not directly associated with specific prescriptions, it is not possible to establish a causal relationship between prescribing practices and specific indications. The definition of a particular time frame between the diagnosis code for chronic pain and the prescription of gabapentinoids has resulted in a reduced patient cohort. Consequently, the reported number of patients with chronic pain who have been prescribed gabapentinoids is expected to be a cautious approximation. Another limitation in diagnosing chronic pain conditions using READ codes is that some have not been validated for accuracy or appropriateness. The codes were selected based on research team discussions and primarily sourced from the ClinicalCodes repository (https://clinicalcodes.rss.mhs.man.ac.uk/). Each code list is linked to articles, mainly peer-reviewed publications or resources like the QOF Business Rule sets.

Additionally, the analysis was conducted utilising prescriptions generated in primary care settings. It is important to note that certain assumptions were made regarding the actual dispensation and consumption of the prescribed medications by patients. These assumptions might have resulted in an overestimation of the overall drug usage statistics. However, it is vital to emphasise that prescription data serves as a key source of information for research efforts in the fields of drug utilisation and pharmacoepidemiology. It is important to be aware of the potential for bias in the methods used to estimate prescription durations and daily dosages. This stems from the complexity associated with medications that are taken as needed—specifically, the inconsistent documentation of intended durations and dosing plans for these types of medications. However, imputation techniques were employed to evaluate the potential impact of these estimations. Finally, the study did not examine the factors

related to the observed changes in prescribing patterns among gabapentinoid drugs. While recognising these limitations, the objective of the study was to obtain approximate figures for prescribing and describe the changes observed over time.

3.5 Conclusion

This study provided an outline of the prescribing patterns of pregabalin and gabapentin for patients with chronic pain, spanning a duration of 16 years. A general upward trend was observed in the number of prescriptions, the number of gabapentinoid users, the average prescribed daily doses, and the duration of supply for prescribed pregabalin and gabapentin over the duration of the study. Subsequently, there has been a progressive decline in the prevalence and incidence rates of individuals using gabapentinoids following the release of the ACMD report in 2016. A marginal reduction in the annual incidence of gabapentinoid users was observed following the reclassification in April 2019.

A significant high number of patients have used gabapentinoids for unlicensed indications of CNCP. This matter is of concern due to the limited evidence supporting their efficacy beyond clearly defined licensed indications and the potential for harm, especially when co-prescribed with other central nervous system depressant medications. The difficulty for clinicians in supporting patients to discontinue gabapentinoid use in UK primary care may be attributed to the limited availability of effective pharmaceutical alternatives and non-pharmacological therapies for chronic pain.

In light of the recent policy change, a thorough reassessment of how gabapentinoids are used has become essential. To accurately determine the exact impact of this reclassification, it is crucial to employ a more focused and effective method that ensures a correct evaluation of its effects. This is key to precisely attributing any decrease in the number of gabapentinoid users to the policy adjustment while separating it from other potential variables that could confound the analysis.

Furthermore, a critical aspect of this research involves examining the potential hazards associated with adverse events related to gabapentinoids. Investigating these risks is crucial for identifying the factors that contribute to negative outcomes. The insights gleaned from such an investigation can pave the way for developing targeted interventions that bolster the appropriateness of gabapentinoid prescription practices and fortify their safety profile. In essence, this comprehensive analysis encompasses multiple dimensions, ranging from policy implications to potential safety concerns, culminating in the development of a nuanced strategy that encompasses the broader landscape and strategically informs the enhancement of prescription practices, thereby contributing to better patient outcomes.

Chapter 4 Impact of gabapentinoid reclassification as a controlled drug on pregabalin and gabapentin utilisation

4.1 Introduction

The preceding chapter examined the prescribing trends and dosing patterns of gabapentinoids in UK primary care from 2005 to 2020, revealing a general upward trend in use for chronic pain. While there may be valid clinical reasons, the rapid rise raises concerns about potential abuse and misuse. Consequently, in October 2018, the UK government announced that gabapentinoids would be classified as Schedule 3 (Class C) controlled drugs starting in April 2019 (GOV.UK, 2018). The impact of this reclassification has not yet been investigated. Therefore, this study aimed to evaluate the effect of gabapentinoid reclassification on drug use before and after the policy's implementation.

4.2 Aim and objectives

The aim of this study was to measure the effect of policy changes in the United Kingdom, particularly the reclassification of gabapentinoid drugs as controlled substances, on their use by patients with chronic pain in primary care. To achieve this, the following objectives were identified and addressed:

(1) Evaluate the impact of gabapentinoid reclassification on the monthly prevalence of PGB and GBP users in patients diagnosed with chronic pain before and after the implementation of gabapentinoid reclassification.

(2) Evaluate the impact of gabapentinoid reclassification on the monthly prescribed daily dose of PGB and GBP in patients with a chronic pain diagnosis before and after the implementation of gabapentinoid reclassification.

The detailed method is described in Chapter 2, Section 2.2.2.

4.3 Results

4.3.1 The impact of gabapentinoids reclassification on monthly prevalence of gabapentin users

The monthly prevalence of gabapentin users per 10,000 registrants exhibited a significant decrease in the baseline trend (β1: -0.032, p= 0.037). The data suggests a decline in the monthly prevalence rate of gabapentin users per 10,000 registrants by -0.032 for each month, while keeping all other variables unchanged as the initial long-term trend. The coefficient β2 was calculated to be 0.67 but was found to be statistically insignificant (p= 0.161), indicating no significant change in the monthly prevalence of gabapentin users per 10,000 registrants immediately after the reclassification. A statistically significant decline of 18% was observed in the monthly prevalence of gabapentin users per 10,000 registrants following the implementation of the reclassification. This change in trend was compared to the trend observed prior to the reclassification, with a coefficient of -0.184 (p= 0.000). These findings are presented in Table 4-1 and Figure 4-1.

4.3.2 The impact of gabapentinoids reclassification on monthly prevalence of pregabalin users

The baseline trend prior to the reclassification of gabapentinoid was -0.004, which was determined not to be statistically significant (p= 0.454). This suggests that there was no notable alteration in the monthly prevalence of pregabalin users per 10,000 registrants before the reclassification of gabapentinoid. There was no statistically significant change in the monthly prevalence of pregabalin users per 10,000 registrants immediately following the reclassification (β2: 1.066, p= 0.120). However, after gabapentinoid was reclassified, there was a noticeable drop of 13% in the

monthly number of patients using pregabalin per 10,000 registrants compared to the previous trend (β3: -0.132, p=0.04) (see Table 4-1 and Figure 4-2).

Table 4-1: The Multiple Segmented Regression Analysis of Interrupted Time Series for Monthly Prevalence of Gabapentinoid Users

Dependent variable	Coefficients	Std. Err.	t	Sig
Monthly prevalence of gabapentin users[1]				
β0 (constant)	13.13146	3.761545	3.49	0.001
β1	-0.032299	0.0152614	-2.12	0.037
β2	0.6736215	0.476942	1.41	0.161
β3	-0.1845971	0.0377528	-4.89	0.000
Monthly prevalence of pregabalin users[2]				
β0 (constant)	10.28569	2.919426	3.52	0.001
β1	-0.004475	0.0059503	-0.75	0.454
β2	1.066158	0.6796433	1.57	0.120
β3	-0.1322808	0.0652522	-2.03	0.04

Std. Err.: Standard error; t: t-value; sig: probability
1 This is the result of Regression after correction of autocorrelation with Newey-West standard errors regression
2 This is the result of Regression after correction of autocorrelation

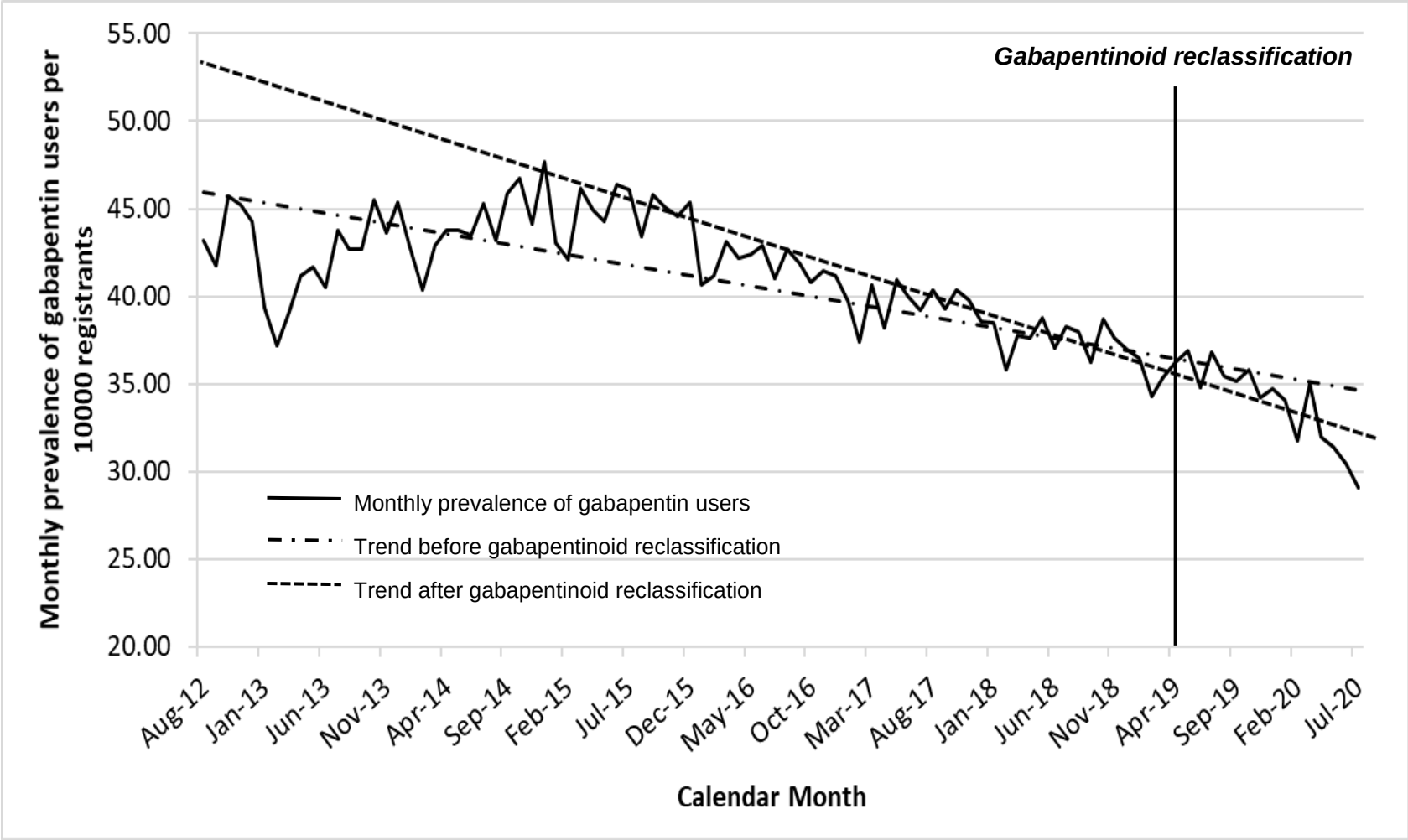


Figure 4-1: Monthly Prevalence of Gabapentin Users per 10,000 Registrants between 2012 And 2020

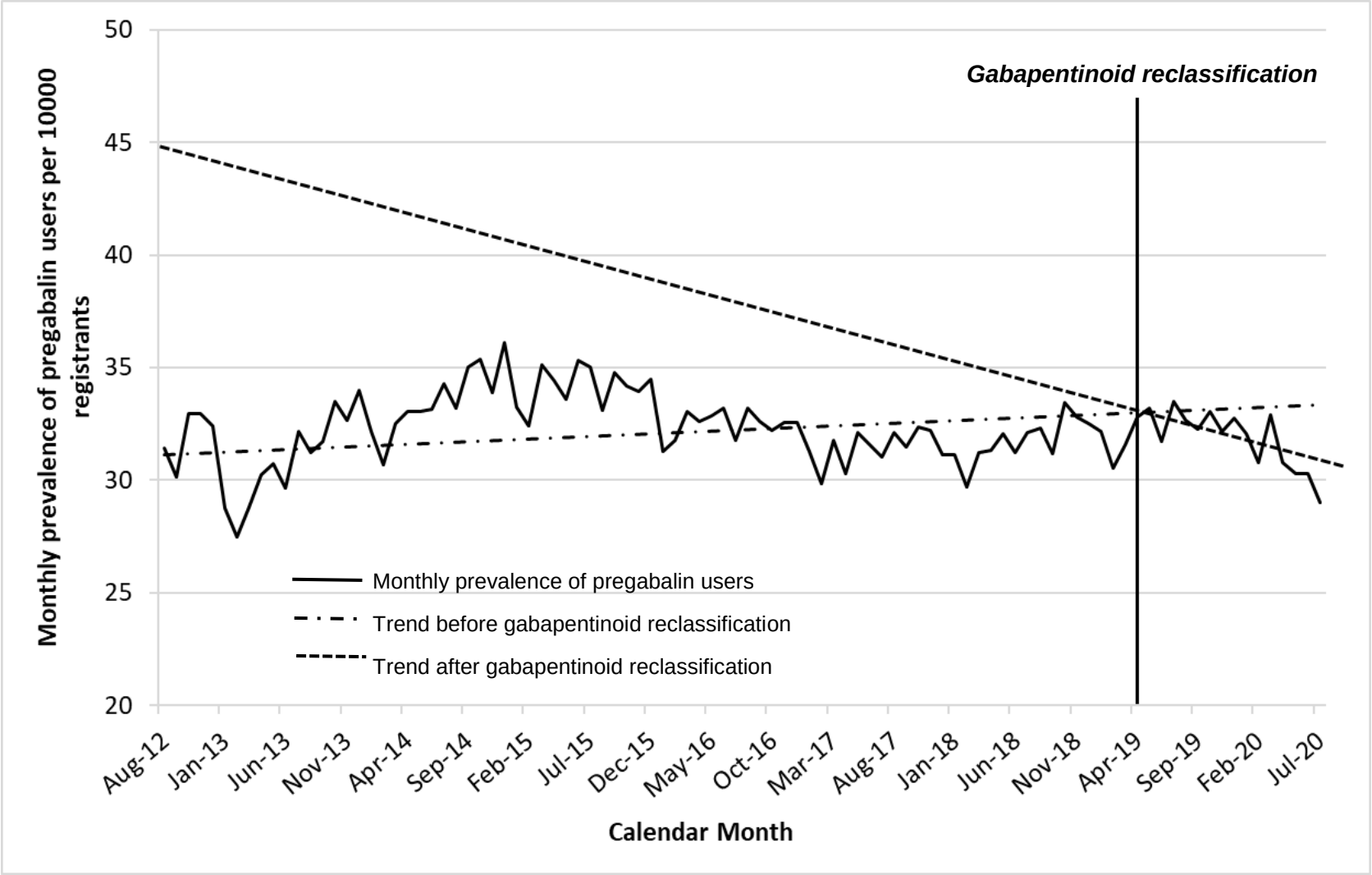


Figure 4-2: Monthly Prevalence of Pregabalin Users per 10,000 Registrants between 2012 And 2020

4.3.3 The impact of additional time points on the monthly prevalence of gabapentinoid users

This analysis evaluated the inclusion of various time points in the policy development process encompass the initial report of pregabalin abuse in January 2013, the publication of advice regarding the risk of gabapentinoid misuse in December 2014, and the ACMD recommendation for the reclassification of gabapentinoid in January 2016. There has been a notable shift in the monthly prevalence of gabapentinoid users. The monthly prevalence of gabapentinoid users began to decline following the release of the ACMD recommendations to control gabapentinoids as a Class C substance and Schedule 3, and this decline persisted after the implementation of the gabapentinoid reclassification policy. The results of the ITS segmented regression analysis model are in Appendix VI.

4.3.4 The impact of gabapentinoids reclassification on monthly prescribed daily dose of gabapentin users

The analysis of the ITS indicated that there was no statistically significant change in the baseline and monthly prescribed daily dose levels. However, there was a consistent decrease in the dose from August 2012 to May 2019 following the implementation of the policy (gabapentinoids reclassification). The regression coefficients for this decrease were β1: -0.08 (p= 0.412) and β2: -0.95 (p =0.932). A statistically insignificant increase was observed in the trend of PDD following the implementation of legalisation from May 2019 to July 2020, as compared to the trend prior to reclassification (β3: 0.11, p=0.913) (refer to Figure 4-3 and Table 4-2). However, the increase in the monthly PDD was within the normal recommended daily dose.

4.3.5 The impact of gabapentinoids reclassification on monthly prescribed daily dose of pregabalin users

The results from the ITS analysis demonstrated a comparable trend to the data illustrating the average monthly PDD of gabapentin. It is worth noting that the monthly PDD of pregabalin was initially low at the baseline and remained at a similar level immediately following the reclassification (β1: -0.009, p=0.804; β2: -1.899, p=0.662). Following the implementation of gabapentinoids reclassification, specifically between May 2019 and July 2020, there was a notable period of decline in the monthly PDD trend. This decline occurred at a relatively rapid pace compared to the trend observed prior to the reclassification (β3: -0.156, p= 0.708). The statistical analysis revealed that the changes in the baseline, level, and trend were not significant (see Figure 4-4 and Table 4-2).

Table 4-2: The Multiple Segmented Regression Analysis of Interrupted Time Series for Monthly-Prescribed Daily Dose of Gabapentinoid Users Models

Dependent variable	Coefficients	Std. Err.	t	Sig
Monthly PDD of gabapentin users				
β0 (constant)	1068.187	104.8772	10.19	0.000
β1	-0.0807786	0.0980528	-0.82	0.412
β2	-0.9579663	11.27514	-0.08	0.932
β3	0.117978	1.077024	0.11	0.913
Monthly PDD of pregabalin users				
β0 (constant)	266.0309	1.717876	154.86	0
β1	-0.00918	0.036848	-0.25	0.804
β2	-1.89927	4.33256	-0.44	0.662
β3	-0.15579	0.414388	-0.38	0.708

PDD: prescribed daily dose; Std. Err.: Standard error; t: t-value; sig: probability

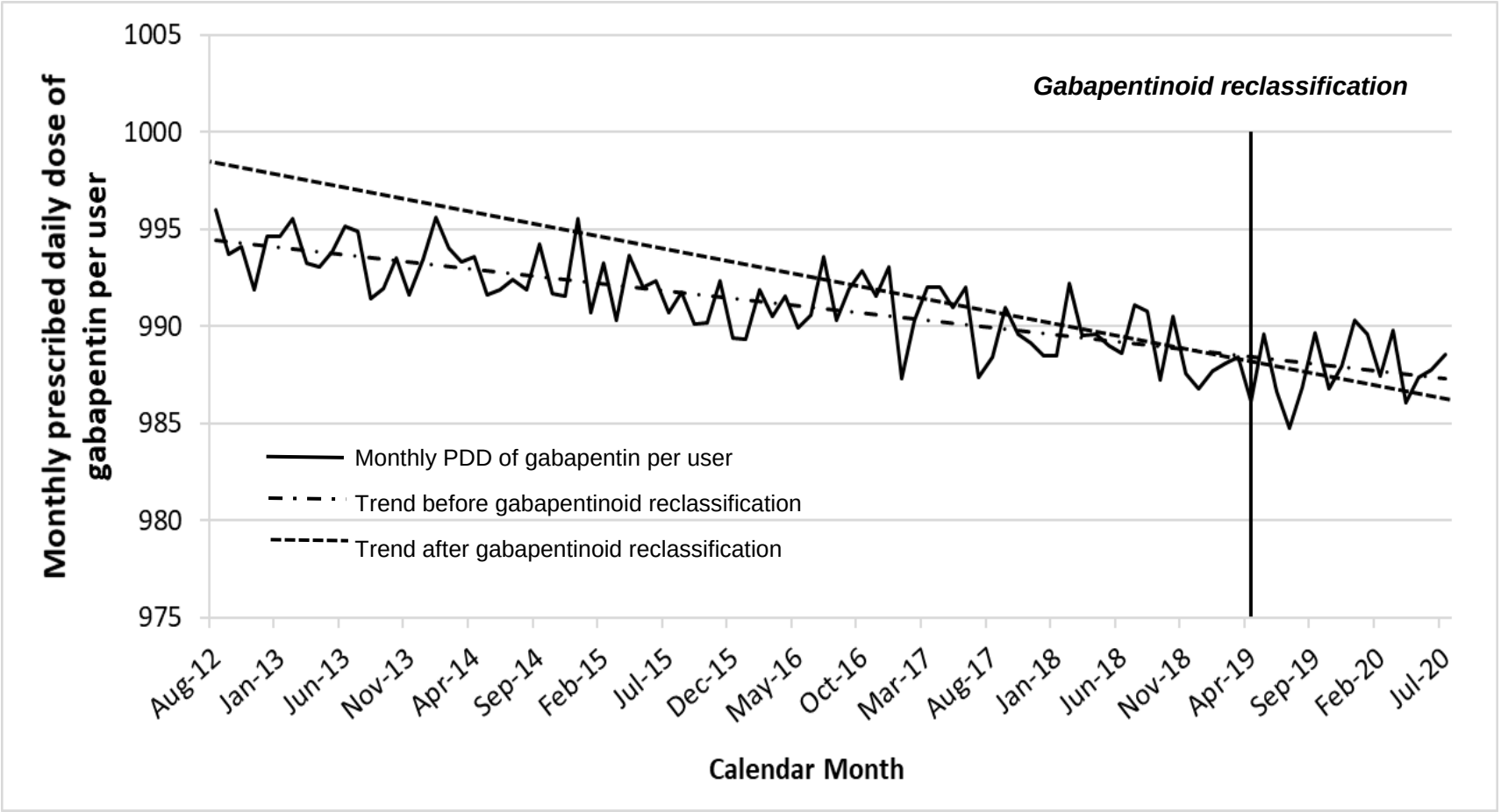


Figure 4-3: Monthly Prescribed Daily Dose of Gabapentin per User between 2012 And 2020

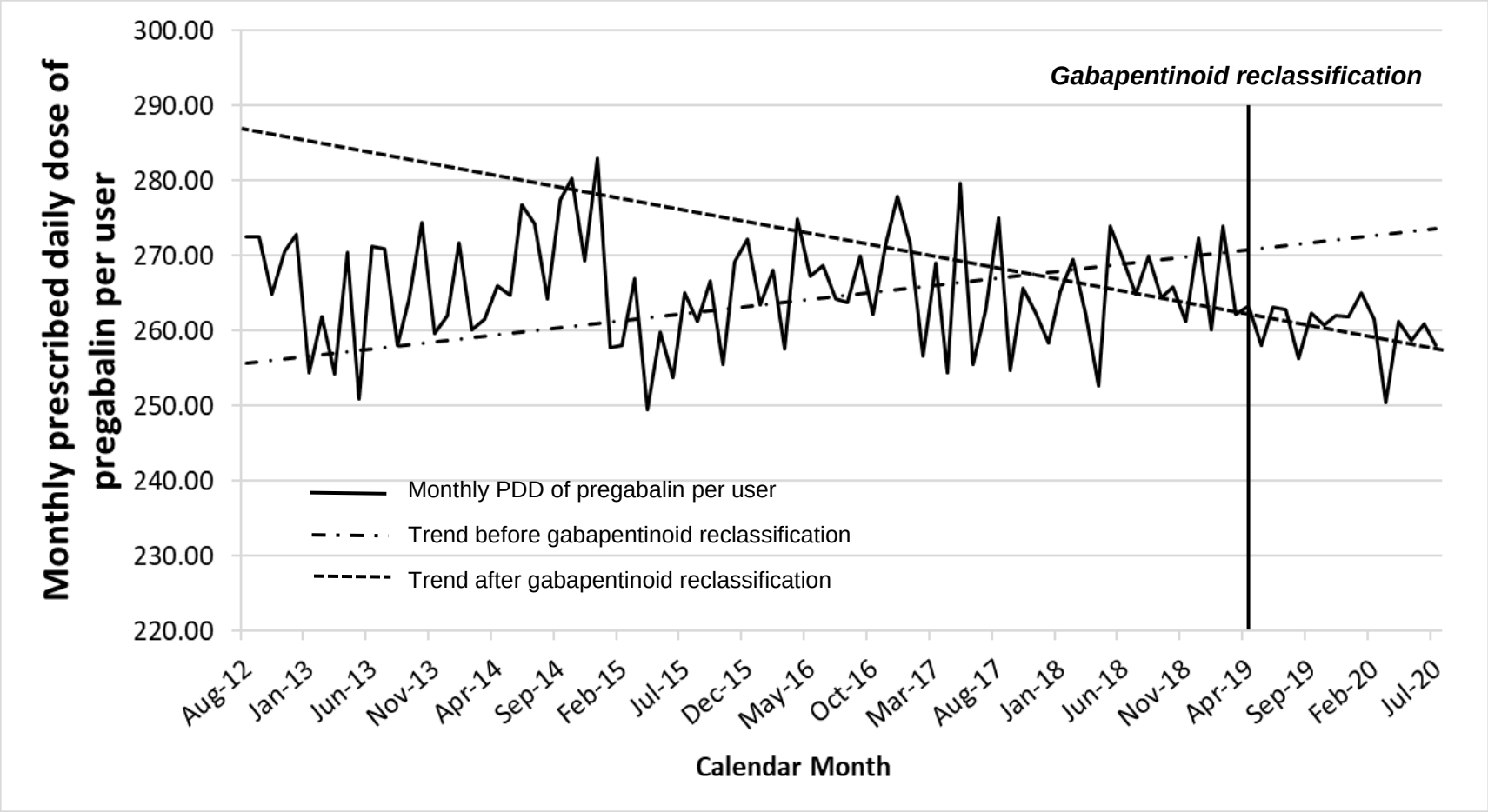


Figure 4-4: Monthly Prescribed Daily Dose of Pregabalin per User between 2012 And 2020

4.4 Discussion

4.4.1 Main findings

The findings of the ITS analysis, as presented in this chapter, indicate that the reclassification of gabapentinoid has resulted in a significant reduction in the monthly prevalence trend of pregabalin and gabapentin users when compared to the trend observed prior to the reclassification. Nevertheless, the underlying trend prior to the reclassification and the monthly prevalence of pregabalin users in the immediate month following the reclassification remained consistent, yielding not statistically significant results. Following the release of ACMD recommendations, there was a decrease in the monthly prevalence of individuals using gabapentinoid, and this decrease has persisted even after the reclassification of gabapentinoid. There were no notable alterations observed in the baseline trend prior to the reclassification or in the level or trend after the reclassification of gabapentinoid in relation to the prescribed daily dose of GBP and PGB. A decrease was observed in the monthly prescribed daily dose for users of pregabalin, while a corresponding increase was noted in the monthly prescribed daily dose for gabapentin. However, these figures were not statistically significant. This increase in gabapentin dosage and decrease in pregabalin dosage may be because gabapentin has a lower propensity for abuse than pregabalin (Bradley, 2016). Additionally, another reason might be that gabapentin received approval as an analgesic before pregabalin did (Bennett and Simpson, 2004).

4.4.2 Comparison with other studies

The findings of the present study demonstrate a significant reduction in the prevalence of individuals who used gabapentinoid for chronic pain management following their reclassification. No studies have assessed the impact of gabapentinoid reclassification on the prevalence rate of gabapentinoid users among patients with chronic pain diagnoses. However, two earlier studies evaluated the impact of the reclassification of gabapentinoids as controlled substances on the prevalence of gabapentinoid prescriptions for all indications. Following the reclassification, a study by Gu et al. (2021) found a notable and gradual decline in the number of prescriptions for GBP and PGB. Another study aimed to analyse the trends of gabapentinoid prescribing in UK primary care, both before and immediately after reclassification. The findings of this study align with those of previous research, indicating that the prevalence of gabapentin and pregabalin began to decline in 2016 and has continued to gradually decrease following the reclassification (Ashworth et al., 2023).

In this study, a decline in the prescribed daily dosage of pregabalin after reclassification was observed. This result is align with a study by Althunaian et al. (2021), which looked at the effects of the Saudi Food and Drug Authority's (SFDA) regulatory restriction to include pregabalin on the controlled substance list. In the study, a significant decrease in PGB dose was observed following policy implementation. This reduction was observed immediately after the policy and continued to decrease gradually every quarter. Subsequently, the observed findings of this study, including the decline in the monthly prevalence of gabapentinoid users and the prescribed daily doses, could potentially be attributed to the introduction of ACMD recommendations and the favourable outcomes

resulting from the implementation of gabapentinoid reclassification. The implementation of this restriction on the use of gabapentin and pregabalin may potentially mitigate the harms linked to their consumption.

4.4.3 Strength and limitation

This study possesses several notable strengths. For instance, it exhibits strength as it examines the impact of gabapentinoid reclassification on gabapentinoid users among chronic pain patients in the United Kingdom. Another aspect that makes this study robust is the duration of the study period, which runs for eight years. This extended period provided a chance to effectively examine and track changes in the patterns of gabapentinoid utilisation for CNCP. Furthermore, it is worth noting that the current study differs from previous drug utilisation studies because of its focus on the extent of gabapentinoid use in GPs for different chronic pain types. Additionally, this study assessed the dosing patterns of gabapentinoid drugs using PDD, making it the first to do so in comparison to other research.

It is important to consider certain limitations. This study utilised prescriptions generated in primary care during the analysis. The primary assumption was that the prescribed medications were dispensed and consumed by patients. However, this assumption may have led to an overestimation of overall drug utilisation. Furthermore, it is important to acknowledge the potential introduction of bias when estimating the duration and daily dose of prescriptions, especially in cases where the intended duration and dosing for 'when required' medications are not consistently recorded. Nevertheless, in order to assess the impact of these estimations, appropriate imputation methods were employed. Additionally, ITS analysis was conducted to explore potential hypotheses regarding the

effect of gabapentinoid utilisation changes. However, it could not establish causal relationships between statistically significant changes in the series and the implementation of interventions (gabapentinoid reclassification) legislation. Any alterations within a series may be attributed to various known or unknown events that transpired concurrently. Nonetheless, the sensitivity analysis evaluated various events or time points that could potentially impact the rate of gabapentinoid utilisation. The observed decrease in the monthly prevalence rate of gabapentinoid users following the implementation of gabapentinoid reclassification may not necessarily be attributed solely to the impact of the reclassification legislation.

4.5 Conclusion

In conclusion, the implementation of gabapentinoid reclassification as controlled C drugs has shown a decrease in the monthly-prescribed daily dose and a statistically significant reduction in the trend of monthly prevalence of GBP and PGB users among patients diagnosed with chronic pain in primary care. Further investigations regarding the potential risks associated with gabapentinoid-related harm, as well as the identification of factors contributing to unfavourable outcomes, are warranted. These investigations will provide valuable insights to guide interventions aimed at improving the appropriateness and safety of gabapentinoid utilisation.

Chapter 5 Association between gabapentinoid use and the risk of overdose in patients with chronic pain

5.1 Introduction

Chapter 3 reported an overall rise in gabapentinoid use, raising concerns about excessive prescribing, especially for unlicensed uses. This increases the risk of adverse effects and potential harm, such as overdose (Cairns et al., 2019; Crossin et al., 2019; Peckham et al., 2018a). Evidence regarding overdose are limited and mainly from case reports and post-mortem toxicology cases. There is also a lack of information on gabapentinoid overdose in the UK general population (Bonnet et al., 2018). Therefore, it is crucial to examine the overdose risk associated with gabapentinoid use in chronic pain patients. This study investigated the link between gabapentinoid use and overdose risk over eight years.

5.2 Aim and objectives

The aims of this study were to determine the number of patients with documented overdose cases in either the CPRD, HES, or both databases, using data from patients whose records were linked between CPRD and HES. Additionally, this study aimed to investigate whether gabapentinoids, when used as analgesics, are associated with the potential risk of overdose in individuals with chronic pain in England.

The specific study objectives were:

(1) To determine the proportion of patients who have recorded cases of overdose within the CPRD or HES databases, or both.

(2) To compare the initial overdose dates recorded in the CPRD or HES for patients who have overdose records in both databases.

(3) To investigate the association between current exposure to gabapentinoid drugs (PGB, GBP, or both) and the risk of overdose in comparison to individuals who are not currently exposed to these medications.

For more details about the method, please refer to Chapter 2, Section 2.2.3.

5.3 Results

5.3.1 HES-linked population

Out of 945 English practices, 356 (37.7%) with HES linkage were eligible and used in this study. The linkage between CPRD and HES covered the period from 1st April 1997 to 31st October 2020. Overall, 316,347 patients with chronic pain were prescribed gabapentinoids between 1st August 2012 and 31st July 2020. A total of 106,129 patients (33.5% out of 316,347) diagnosed with chronic pain and prescribed gabapentinoids during the research period were eligible for linkage. Of these 106,129 individuals, 78,787 (74.2%) had been prescribed at least two consecutive gabapentinoid prescriptions, while 27,342 (25.8%) had been prescribed only one. Among the 78,787 individuals, 41,707 (52.9%) were prescribed gabapentin, 22,310 (28.3%) were prescribed pregabalin, and 14,770 (18.7%) were prescribed both medicines, having switched between the two drugs.

The majority of users were female (61.9%–66.4%), and the median ages were 59 years for the gabapentin sample, 57 years for the pregabalin sample, and 56 years for the sample using both. Compared to the other categories, gabapentin users were most numerous in the least deprived IMD category (7,549; 18.1%) and in the most deprived category (9,203; 22.1%). Depression was the most common comorbidity recorded within one year before starting gabapentinoid prescription among the three exposure groups (13.4%). The majority of the population was prescribed antidepressants alongside gabapentinoids (gabapentin: 44%; pregabalin: 47%; both: 51%). Pregabalin users, when compared to the other groups, had the highest proportion of SUD diagnoses (Table 5-1).

Table 5-1: Characteristics of the Study Cohort (N=78,787) Stratified by Drug Class, Values are Numbers of Patients (%) Unless Stated Otherwise

Patient Characteristics	Gabapentin n=41,707	Pregabalin n=22,310	Both[c] n=14,770
Gender [a]			
Male	15,898 (38.1)	8,300 (37.2)	4,959 (33.6)
Female	25,809 (61.9)	14,010 (62.8)	9,810 (66.4)
Age at baseline (years)*			
Median (IQR)	59 (47-72)	57 (45-71)	56 (44-69)
Range	18-106	18-105	18-99
Age rank			
18-30	1,919 (4.6)	1,406 (6.3)	903 (6.1)
31-40	3,880 (9.3)	2,483 (11.1)	1,754 (11.9)
41-50	7,312 (17.5)	4,310 (19.3)	3,108 (21)
51-60	8,751 (21)	4,354 (19.5)	2,958 (20)
61-70	8,483 (20.3)	4,047 (18.1)	2,713 (18.4)
71-80	7,068 (17)	3,399 (15.2)	2,303 (15.6)
>80	4,294 (10.3)	2,311 (10.4)	1,031 (7)
IMD score (% from total)			
Missing	46 (0.11)	14 (0.06)	10 (0.07)
1 (least deprived)	7,549 (18.1)	4,479(20.1)	2,669 (18.1)
2	7,645 (18.3)	4,298(19.3)	2,699 (18.3)
3	8,658 (20.8)	4,582 (20.5)	3,014 (20.4)
4	8,606 (20.7)	4,442 (19.9)	3,135 (21.2)
5 (most deprived)	9,203 (22.1)	4,495 (20.2)	3,243 (22)
Comorbidities at baseline [b]			
Cardiovascular disease	1316 (3.2)	665 (3)	361 (2.4)
Diabetes	956 (2.3)	550 (2.5)	324 (2.2)
COPD	964 (2.3)	466 (2.1)	305 (2.1)
Stroke	749 (1.8)	482 (2.2)	242 (1.6)
Anxiety	674 (1.6)	1,057 (4.7)	364 (2.5)
Depression	1,445 (3.5)	1,234(5.5)	645 (4.4)

Patient Characteristics	Gabapentin n=41,707	Pregabalin n=22,310	Both[c] n=14,770
Other characteristics at baseline			
Patients with SUD [d]	1,227 (2.9)	1,078 (4.8)	567 (3.8)
Using overdose risk increasing drugs [e]			
benzodiazepines	2,648 (6.4)	1,717 (7.7)	1,093 (7.4)
opioids	14,012 (33.6)	6,890 (30.9)	4,874 (33)
z-drugs	1,488 (3.6)	1,084 (4.9)	612 (4.1)
Antidepressant	18,458 (44.3)	10,551 (47.3)	7,544 (51.1)

COPD– Chronic obstructive pulmonary disease; IMD – index of multiple deprivations; IQR – interquartile range; SUD – substance use disorder
*Calculated at the start of gabapentinoid treatment;
a- One patient was indeterminate in regard to gender type;
b- Comorbidity was within one year before the start gabapentinoid treatment;
c- One patient was indeterminate in regard to gender type
d- History of substance use disorder within one year prior to start of gabapentinoid prescription
e- Overdose risk increasing drugs at least one prescription of these drugs within 1-year prior start of gabapentinoid treatment.

5.3.2 Number and proportion of overdose cases in CPRD, APC HES or both

Out of the total linked patients (n = 78,787), 2,185 (2.8%) had an overdose recorded within the study period. Among these patients, 295 (0.3%) had an overdose recorded only in the CPRD (group 1), and 1,557 (1.98%) had an overdose record only in HES data (group 2). Additionally, 333 patients (0.4%) had an overdose record in both databases (group 3), while 76,602 (97.2%) did not have an overdose record in either database (group 4). The majority of overdose cases were included in the HES database. Figure 5-1 summarises the method of identifying each of the four groups.

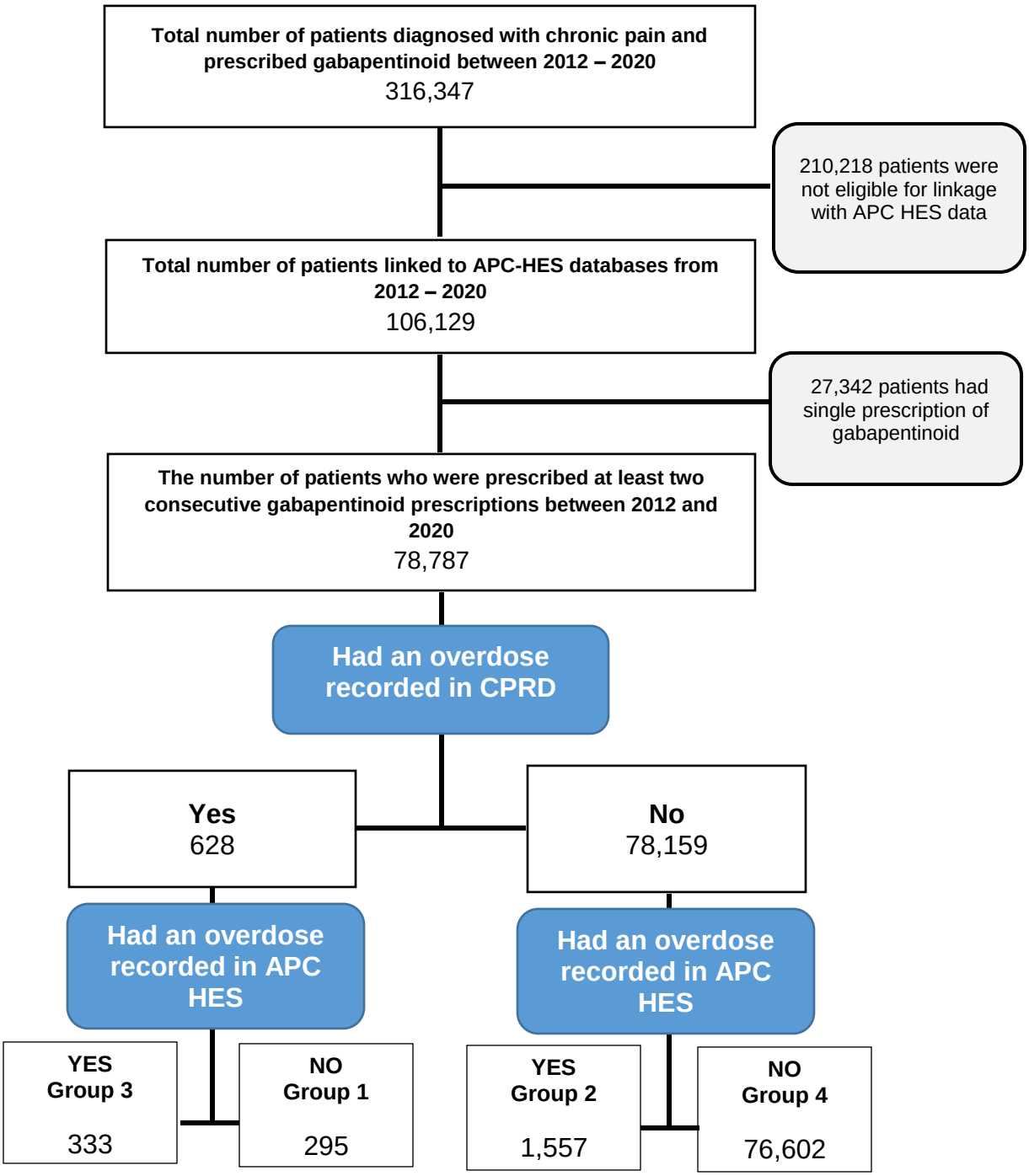


Figure 5-1: Flow Diagram Outlining the Process of Group Identification According to the Existence of an Overdose Record in CPRD, HES or Both

5.3.3 Comparison of dates of overdose recording in both database (CPRD – APC HES)

Out of the 2,185 patients, 333 (15.2%) had an overdose recorded in both databases. The time gap between the two overdose dates was determined by analysing the records of patients with an overdose documented in both the CPRD and HES databases. The date of the first overdose after the start of gabapentinoid treatment was selected for comparison, and the results are summarised in Table 5-2.

Table 5-2: Time Gap between Overdose Recording Dates in CPRD and HES Datasets, Gap Category and Number of Patients in Each Database

Time Gap Category (Days of Gap in Recording Between CPRD and HES)	**Number of Patients with a Record of Overdose in both datasets N= 333**
No gap (same recording date in CPRD and HES)	169 (50.8%)
Very short gap (≤ 2days)	74 (22.2%)
Short gap (> 2 days and ≤7days)	28 (8.4%)
Intermediate gap (>7 days and ≤14 days)	5 (1.5%)
Long gap (> 14 days and ≤30 days)	6 (1.8%)
Prolong gap 1 (>30 and ≤60 days)	6 (1.8%)
Prolong gap 2 (>60 and ≤90 days)	4 (1.2%)
Prolong gap 3 (>90 days)	41 (12.3%)
Dataset first recorded	**Number of Patients with a Record of Overdose in both datasets N= 333**
Number of overdose events first recorded in HES	98 (29.4%)
Number of overdose events first recorded in CPRD	66 (19.8%)

CPRD: Clinical Practice Research Datalink; HES: Hospital episode statistics

Of the 333 overdose records, 169 patients (50.8%) had their overdoses recorded on the same day in both databases. Additionally, 113 overdose records (33.9%) were recorded

within a month of one another, excluding those recorded on the exact same date. Furthermore, 51 overdose events (15.3%) were recorded with a delay of more than a month between the two dates. The overdose records for 98 participants were first recorded in HES data, with a median delay of 3 days (IQR 1-9) before being transferred to the GP system. For the patients who first had an overdose record documented in primary care (n = 66), the median delay in recording overdose dates between primary and secondary care data was 47.5 days (IQR 1-566) (Table 5-2).

5.3.4 Number and proportion of gabapentinoid users and prescriptions

A total of 1,737,073 gabapentinoid prescriptions were issued over the eight years during which the study was conducted. The number of patients prescribed each drug, as well as the number of prescriptions, are presented in Table 5-3. Within the study population, 52.9% (n = 41,707) were prescribed gabapentin, 28.3% (n = 22,310) were prescribed pregabalin, and 18.8% were prescribed both (switching between pregabalin and gabapentin) (n = 14,770) (Table 5-3). Patients prescribed pregabalin had the highest average number of prescriptions per patient over the study period, with 13 prescriptions each (Table 5-3).

Table 5-3: Number of Patients and Prescriptions Diagnosed with Chronic Pain by Exposure Group during the Study Period (8 Years)

Exposure group	Number of patients N=78,787		Number of Prescriptions N= 1,737,073		Median number of prescriptions per patient
	(n)	(%)	(n)	(%)	n (IQR)
Gabapentin	41,707	52.9	795,657	45.8	8 (3, 22)
Pregabalin	22,310	28.3	591,048	34	13 (4, 32)
Both	14,770	18.8	350,368	20.2	11 (4, 30)

IQR: Inter Quartile Range

5.3.5 Follow up time

The median follow-up days for each exposure group are detailed in Table 5-4. Those who used pregabalin had the longest duration of follow-up, with a median of 2241 days (approximately 6.1 years), and an IQR of 1060 to 2874 days (approximately 2.9 to 7.9 years) (Table 5-4).

Table 5-4: Follow-Up Days and Years by Exposure Group

Exposure group	Median Days of Follow-up (yrs.)	IQR (25%, 75%) (yrs.)
Gabapentin	2104 (5.8 yrs.)	(1236, 2654) (3.4, 7.5)
Pregabalin	2241 (6.1 yrs.)	(1060, 2874) (2.9, 7.9)
Both	2205 (6 yrs.)	(1456, 2703) (4, 7.4)

IQR: Inter Quartile Range; yrs.: years

5.3.6 Characteristics of patients who experienced an overdose among HES linked population

During follow-up, a total of 2,185 patients, representing 2.8% of the total linked sample of 78,787 patients, experienced an overdose. The demographic, socioeconomic, and clinical characteristics of patients with an overdose record throughout the study period

are displayed in Table 5-5. Most participants who experienced an overdose were female, particularly in the gabapentin group, where over half of the participants (n = 556) were female. Middle-aged patients (41–50 years) constituted the highest proportion of those experiencing an overdose (23.8% in the gabapentin group, 27.2% in the pregabalin group, and 26.7% in both group). Across the three exposure groups, the majority of patients with an overdose were in the most deprived IMD category.

Depression was the most prevalent comorbidity among patients who experienced an overdose, a trend consistent across all three exposure groups. Nearly half of these patients were concurrently prescribed an antidepressant along with their gabapentinoid. Opioids emerged as the second most common co-prescribed medication in patients with overdose records, featuring in 38.6% of gabapentin cases, 28.1% of pregabalin cases, and 29.9% of cases where both drugs were used. Notably, less than 20% of overdose patients had been diagnosed with a substance use disorder, as detailed in Table 5-5.

Table 5-5: Demographic and Clinical Characteristics of Patients with Overdose Records among HES-Linked Population (N=2,185)

Patient Characteristics	Gabapentin n=866 (%)	Pregabalin n=821(%)	Both[c] n= 498 (%)
Gender [a]			
Male	310 (35.8)	311 (37.8)	180 (36.1)
Female	556 (64.2)	511 (62.2)	317 (63.7)
Age at baseline (years)*			
Median (IQR)	51 (40 -67)	47(37-60)	47(38-60)
Range	18-94	18-90	18-93
Age rank			
18-30	80 (9.2)	113 (13.8)	68 (13.7)
31-40	137 (15.8)	156 (18.98)	90 (18.1)

Patient Characteristics	Gabapentin n=866 (%)	Pregabalin n=821(%)	Both[c] n= 498 (%)
41-50	206 (23.8)	223 (27.1)	133 (26.7)
51-60	145 (16.7)	135 (16.4)	86 (17.3)
61-70	130 (15)	91 (11.1)	55 (11)
71-80	103 (11.9)	61 (7.4)	47 (9.4)
>80	65 (7.5)	43 (5.2)	19 (3.8)
IMD score (% from total)			
Missing	1 (0.12)	1 (0.12)	-
1 (least deprived)	104 (12.01)	112 (13.6)	46 (9.2)
2	111(12.8)	137 (16.7)	81 (16.3)
3	163 (18.8)	157 (19.1)	97 (19.5)
4	202 (23.3)	182 (22.1)	108 (21.7)
5 (most deprived)	285 (32.9)	233 (28.4)	166 (33.3)
Comorbidities at baseline [b]			
Cardiovascular disease	32 (3.7)	23 (2.8)	7 (1.4)
Diabetes	23 (2.7)	27 (3.3)	19 (3.8)
COPD	38 (4.4)	16 (1.9)	13 (2.6)
Stroke	19 (2.2)	14 (1.7)	6 (1.2)
Anxiety	28 (3.2)	81 (9.9)	32 (6.4)
Depression	79 (9.1)	101 (12.3)	44 (8.8)
Other characteristics at baseline			
Patients with SUD [d]	152 (17.6)	163 (19.8)	91 (18.3)
Using overdose risk increasing drugs [e]			
benzodiazepines	71 (8.2)	108 (13.1)	48 (9.6)
opioids	334 (38.6)	231 (28.1)	149 (29.9)
z-drugs	50 (5.6)	67 (8.2)	37 (7.4)
Antidepressant	387 (44.7)	399 (48.5)	255 (51.2)

COPD– Chronic obstructive pulmonary disease; IMD – index of multiple deprivations; IQR – interquartile range; SUD – substance use disorder
*Calculated at the start of gabapentinoid treatment;
a- One patient was indeterminate in regard to gender type;
b- Comorbidity was within one year before the start gabapentinoid treatments;
c- One patient was indeterminate in regard to gender type;
d- History of substance use disorder within one year before start of gabapentinoid prescription
e- Overdose risk increasing drugs at least one prescription of these drugs within one year prior the start of gabapentinoid treatment

5.3.7 Number and proportion of patients who had experienced an overdose

The number of patients who experienced an overdose, stratified by exposure treatment groups, is presented in Table 5-6. The proportion of patients with a recorded overdose during the study period varied across these groups, ranging from 1.2% among users of both drugs to 3.7% in the pregabalin-only group (Table 5-6). Among these groups, the gabapentin-only group had the highest number of recorded overdose cases within the study period, totalling 866 (2.1%) (Table 5-6). Table 5-7 details the number of patients who experienced an overdose event in both exposed and non-exposed periods. Notably, the pregabalin group showed a higher number of overdose cases in the exposed period compared to other groups, as demonstrated in Table 5-7.

Table 5-6: Number of Patients Who Experienced Overdose by Exposure Group

Event	Gabapentin group N=41,707 (%)	Pregabalin group N=22,310 (%)	Both group N=14,770 (%)
Patients who experienced an overdose	866 (2.1%)	821 (3.7%)	498 (3.4%)

Table 5-7: Number (%) of Overdose Events by Exposure Periods

Event	Gabapentin group N=866	Pregabalin group N=821	Both group N= 498
Overdose events in the exposed period	396 (45.7%)	428 (52.1%)	236 (47.4%)
Overdose events in non-exposed period	470 (54.3%)	393 (47.9%)	262 (52.6%)

Patients who did not experience any overdose were censored at the earliest of the following dates: date of death, date of leaving the practice (transfer-out date), or the study end date. Table 5-8 displays the reasons for censoring patients who did not experience an overdose. The most common cause of censoring was the end of the study period without experiencing an overdose, accounting for more than 50% of cases across all exposure groups (Table 5-8).

Table 5-8: The Cause and Number of Censored Patients by Exposure Group

Cause of censoring	Gabapentin group N= 40,841 (%)	Pregabalin group N=21,489 (%)	Both group N=14,272 (%)
Death	3,212 (7.9%)	2,027 (9.4%)	829 (5.8%)
Transfer out	4,513 (11.1%)	2,619 (12.2%)	1,286 (9.01%)
End of the study	33,116 (81.1%)	16,843 (78.4%)	12,157 (85.2%)

5.3.8 Cox proportional regression defined as a time-varying exposure

This section reports the results of the main analysis, which applied a Cox proportional hazards model to examine the association between gabapentinoid use and the risk of overdose in patients diagnosed with chronic pain. Initially, a graphic assessment of survivor function and statistical testing for the equality of survivor functions, as well as the assessment of the proportional hazards assumption, are presented. Subsequently, the results concerning the association between gabapentinoid use and the risk of overdose are detailed, both as unadjusted and adjusted HRs with 95% CI.

5.3.8.1 Graphical assessment of survivor function

A Kaplan-Meier curve illustrating survivor functions has been generated for each of the three exposure groups, as shown in Figures 5-2, 5-3, and 5-4. The data presented in these plots indicate that the risk of overdose was higher during the exposed period compared to the non-exposed period across all three groups (gabapentin, pregabalin, and both).

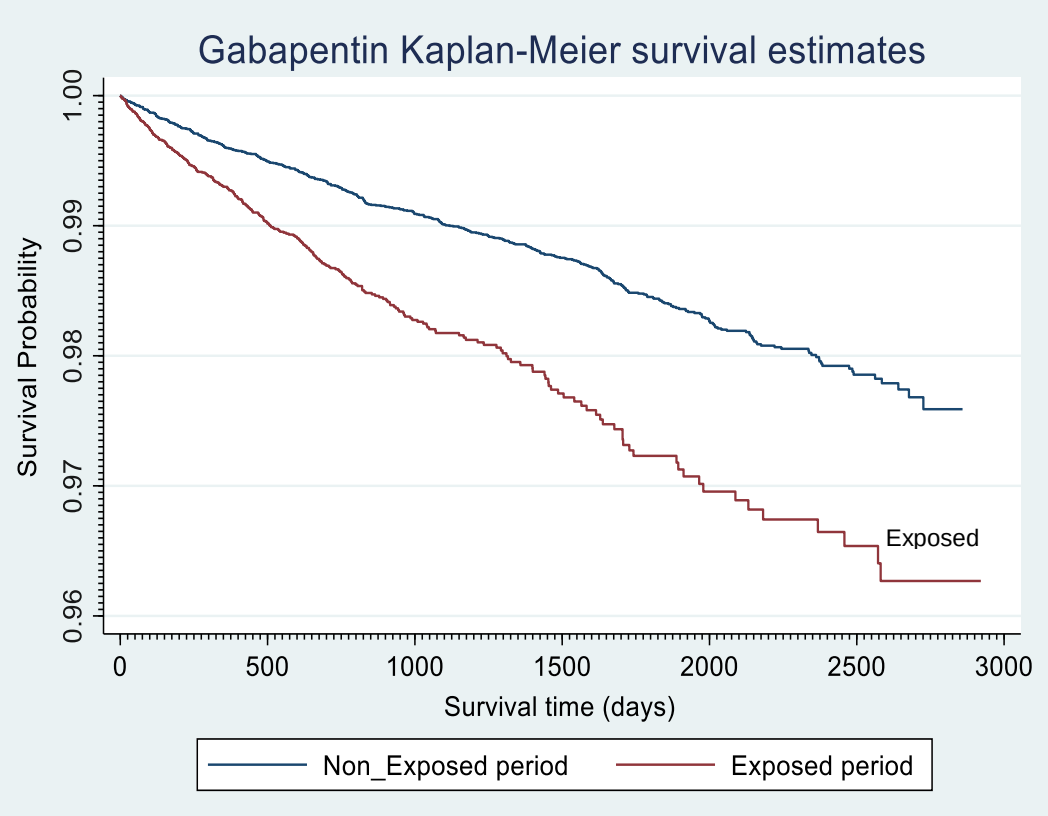


Figure 5-2: Kaplan Meier Survival Estimates for Exposed and Non-Exposed Periods in Gabapentin Group Users

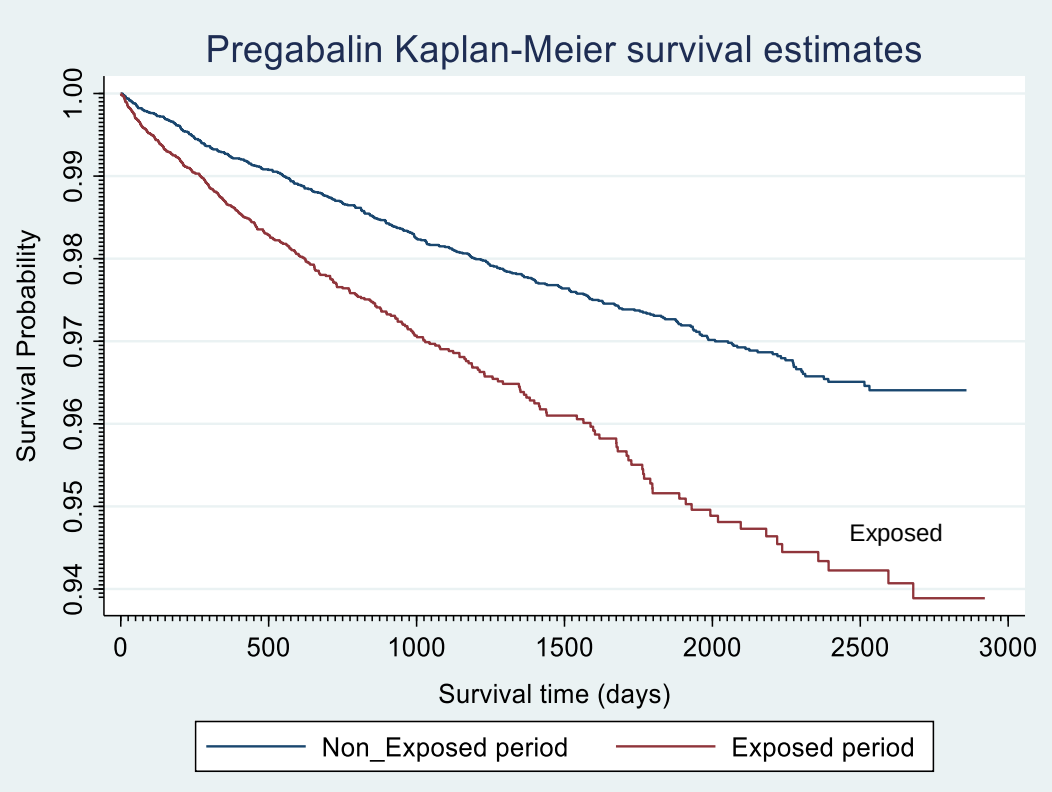


Figure 5-3: Kaplan Meier Survival Estimates for Exposed and Non-Exposed Periods in Pregabalin Group Users

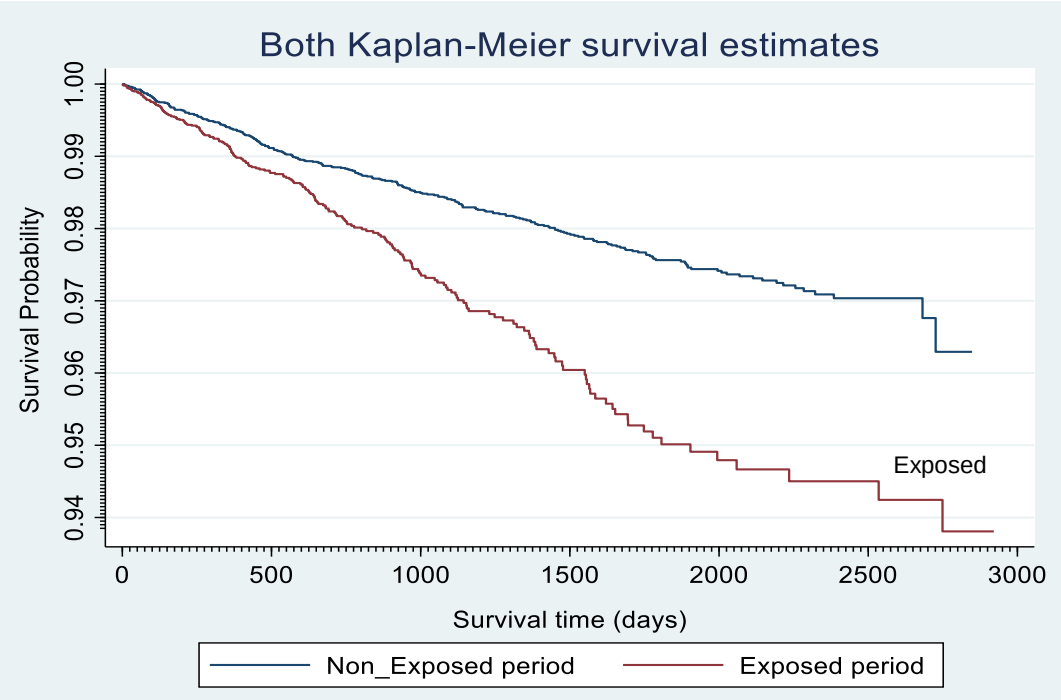


Figure 5-4: Kaplan Meier Survival Estimates for Exposed and Non-Exposed Periods in Both Group Users

5.3.8.2 Statistical assessment of the equality of survivor function

The log-rank test for the statistical assessment of the equality of survival functions indicates a statistically significant difference ($p<0.001$) in survival, specifically the occurrence of overdose, between the exposed and non-exposed periods across the three exposure groups. Consequently, the null hypothesis can be rejected.

5.3.8.3 Cox proportional hazards regression

A separate model was applied to each exposure group, and the corresponding unadjusted HRs with 95% CIs are presented in Table 5-9. These unadjusted HRs indicated a significant association between gabapentinoid use across the three exposure groups and the risk of overdose. Notably, the highest unadjusted HR for overdose was observed in the gabapentin group (HR-unadjusted: 1.81 [95% CI: 1.57, 2.08]) (Table 5-9).

Table 5-9: Current Use of Gabapentinoid and the Risk of Overdose

Exposure group	HR-Unadjusted	95% CI
Non-exposure	Reference	-
Gabapentin	1.81	(1.57, 2.08)
Pregabalin	1.72	(1.49, 1.99)
Both	1.78	(1.48, 2.13)

HR: hazard ratio; CI: confidence interval

5.3.8.3.1 Proportionality of hazards assumption

The proportionality of hazards assumption was assessed both graphically, using Kaplan-Meier analysis, and statistically, through the Schoenfeld residuals test. The Kaplan-Meier curves displayed parallel lines with no evidence of intersection between the evaluated

periods (Figures 5-2, 5-3, and 5-4). Further statistical analysis was conducted to assess the proportionality of hazards assumption. Specifically, the Schoenfeld residuals test for gabapentin yielded a non-statistically significant result (chi-square value of 1.59, p-value = 0.2080). For pregabalin, the test resulted in a chi-square value of 0.30 and a corresponding p-value of 0.5868. In the both exposure group, the global test showed a chi-square value of 2.48 with a p-value of 0.1149, which is also not statistically significant. Consequently, there is insufficient evidence to reject the proportional hazards assumption for all three exposure groups.

5.3.8.3.2 Effect of confounders on the risk of overdose

The objective was to identify potential confounders that changed the HR by ±10%. These confounders included age, gender, deprivation score, SUD, drugs that might increase the risk of overdose, and comorbidities. Each was sequentially added to the Cox regression model. The observed changes in the HR are detailed in Table 5-10. There was variability in the impact of potential confounding variables on the HR across the three distinct exposure groups. Specifically, the IMD score for gabapentin and a history of SUD significantly affected the HR, resulting in an approximate 10% change across all three exposure groups. Consequently, these variables were incorporated as predetermined potential confounders in the final, fully adjusted model.

Table 5-10: The Results of Univariate Analysis Presented the Effect of Potential Confounders on Unadjusted Hazard Ratios for overdose by Exposure Groups

Covariate	Gabapentin	Pregabalin	Both
	HR (95% CI)	HR (95% CI)	HR (95% CI)
HR Unadjusted (95% CI)	**1.81 (1.57, 2.08)**	**1.72 (1.49, 1.99)**	**1.78 (1.48, 2.13)**
A priori confounders*	1.74 (1.51 - 2.01)	1.67 (1.45 - 1.93)	1.75 (1.46 - 2.11)
Gender + PC	1.74 (1.51 - 2.01)	1.67 (1.45 - 1.93)	1.75 (1.46 - 2.11)
Age at the start of the treatment + PC	1.80 (1.57 - 2.08)	1.73 (1.50 - 2.00)	1.74 (1.45 - 2.09)
IMD score + PC	1.69 (1.48 - 1.96)	1.67 (1.45 - 1.93)	1.71 (1.43 - 2.06)
SUD + PC	1.64 (1.43 - 1.89)	1.57 (1.37 - 1.81)	1.64 (1.37 - 1.97)

* Priori confounders include comorbidity and the use of overdose increasing medication. CI: Confidence interval; HR: Hazard ratio; IMD: index of multiple deprivation; PC: a priori confounders; SUD: substance use disorder

5.3.8.3.3 Final Adjusted Model

The results of the adjusted HRs with 95% CIs for the risk of overdose, including each covariate, are presented in Table 5-11. The risk of overdose during the exposed period remained significantly higher than in the non-exposed period across all exposure groups. The HRs before and after adjustment were as follows: for gabapentin, the unadjusted HR was 1.81 (95% CI: 1.57 - 2.08), which adjusted to 1.61 (95% CI: 1.40 - 1.86); for both group, the unadjusted HR was 1.78 (95% CI: 1.48 - 2.13), adjusting to 1.64 (95% CI: 1.37 - 1.97); and for pregabalin, the unadjusted HR was 1.72 (95% CI: 1.49 - 1.99), adjusting to 1.57 (95% CI: 1.37 - 1.81) (Table 5-11).

Table 5-11: Multivariable Analysis Results Presented the Unadjusted and Adjusted Hazard Ratios by Exposure Groups

Exposure group	Unadjusted	Adjusted
	HR (95% CI)	HR (95% CI)
Non-exposure	1.0 (reference)	1.0 (reference)
Gabapentin[a]	1.81 (1.57 - 2.08)	1.61 (1.40 - 1.86)
Pregabalin[b]	1.72 (1.49 - 1.99)	1.57 (1.37 - 1.81)
Both[c]	1.78 (1.48 - 2.13)	1.64 (1.37 - 1.97)

CI: Confidence interval; HR: Hazard ratio
a Adjusted for IMD score, SUD, concomitant use of other increasing risk drugs, comorbidity
b Adjusted for SUD, concomitant use of other increasing risk drugs, comorbidity
c Adjusted for SUD, concomitant use of other increasing risk drugs, comorbidity

The sensitivity analysis results, showing the adjusted HRs with 95% Cis for the risk of overdose with each potential confounding variables, are presented in Table 5-12. These results are based on using different definitions of the exposed period: extending the end of an exposed period to three months (90 days) and reducing it to one month (30 days) after the last collected prescription. Across the exposure groups, the HR for gabapentin varied with these altered definitions. Under the first definition (90 days), the HR for gabapentin increased by 14%. However, under the second definition (30 days), it decreased by 11%. In the pregabalin exposure group, there was a 12% increase in the HR under the first definition, while a 2% decrease was observed under the second definition. For both exposure group, there was a 4% increase in the HR when the exposed period was defined as 30 days and a 2% increase when defined as 90 days after the last collection date.

Table 5-12: Sensitivity Analyses: the Associations between Gabapentinoid Treatment and Overdose by Exposure Groups and Different Definitions of Exposed Period

Exposure group	Adjusted HR (95% CI)
Non-exposure	1.0 (Reference)
Exposure periods of 90 days after the last the collected prescription	
Gabapentin[a]	1.75 (1.53 - 2.02)
Pregabalin[b]	1.69 (1.47 - 1.96)
Both[c]	1.66 (1.39 - 1.99)
Exposure periods of 30 days after the last the collected prescription	
Gabapentin[a]	1.50 (1.30 - 1.73)
Pregabalin[b]	1.55 (1.35 - 1.80)
Both[c]	1.68 (1.40 - 2.02)

CI: Confidence interval; HR: Hazard ratio
a Adjusted for IMD score, SUD, concomitant use of other increasing risk drugs, comorbidity
b Adjusted for SUD, concomitant use of other increasing risk drugs, comorbidity
c Adjusted for SUD, concomitant use of other increasing risk drugs, comorbidity

5.4 Discussion

5.4.1 Main findings

This study examined overdose events documented in the CPRD, HES, and both databases, focusing on individuals diagnosed with chronic pain who were prescribed gabapentinoids. Of the total patients prescribed gabapentinoids for chronic pain, 33.5% (106,129 patients) had linked data. The study included 78,787 (74.2%) of these 106,129 individuals, who had received at least two consecutive gabapentinoid prescriptions. A total of 2,185 overdose occurrences were identified using CPRD-HES-linked data, of which 1,557 overdose events, or 71.3% of all overdose events, were recorded only in HES. However, a relatively small proportion of all overdose events, amounting to 13.5% (295 cases), were reported solely in the CPRD.

Among patients who recorded overdose events in both databases, 33.9% experienced their overdoses within a one-month timeframe, while 12.3% had overdose dates that were more than 90 days apart. Approximately 28.7% of overdose cases handled in hospitals were not recorded in the CPRD. The study's results revealed that utilising HES data substantially increased the identification of overdose events. These findings suggest that the use of record linking could potentially enhance the sensitivity of overdose identification.

Overdose events are typically recorded and managed within secondary care settings, which include hospital medical care and mental health services. In these environments, healthcare professionals play a pivotal role in the prevention and management of overdoses, as outlined in the clinical guidelines and quality standards for self-harm

established by NICE in 2011 (NICE, 2011). Some individuals seek medical attention in primary care settings following an incident of self-harm. It is crucial for healthcare professionals to assess potential physical harm and evaluate the emotional and psychological well-being of these patients before deciding on referral to the emergency department. General practitioners and other primary care clinicians primarily hold the responsibility of referring individuals at risk of recurrent self-harm, such as overdose and poisoning, to community mental health services for further evaluation and treatment. Furthermore, they are tasked with assessing the physical health of individuals who engage in self-harm.

The majority of overdose cases recorded in this study were found within the HES database. However, a limited number of overdose cases (13%) were recorded exclusively in the CPRD database. This discrepancy may be attributable to the variable severity of the outcome (overdose), as most patients experiencing an overdose will seek treatment at a hospital or emergency department. Encounters in secondary care are then documented in primary care records. Nonetheless, a delay in this process is anticipated, as the information needs to be integrated into the primary health records. The presence of an overdose recorded in the CPRD suggests that the patient may initially seek care at a GP surgery and subsequently be referred to the A&E department. Following evaluation, the patient may be discharged without the need for further hospitalisation or ongoing treatment. This scenario could explain why some overdose cases are recorded in the CPRD database.

There were several patient characteristics that might increase the risk of overdose events. Gabapentinoid treatment in middle-aged patients (41-50 years) was associated with the highest risk of overdose, followed by those aged 31 to 40 years. However, the association with overdose decreased among older cohort members (>51 years). In all exposure categories, the majority of individuals who suffered an overdose were female. This trend was particularly noticeable in the gabapentin group, where females accounted for more than half of the participants. Among the three exposure groups, most patients who experienced an overdose were in the most deprived IMD category. The most commonly observed comorbidities among these patients were depression and anxiety, regardless of the exposure level. The most frequently co-prescribed medications across the three groups were antidepressants and opioids. Less than one-fifth of the patients with a history of SUD were associated with overdose cases.

The findings of this study suggest that all examined exposure groups exhibited a heightened risk of overdose compared to periods of non-use in this cohort of patients diagnosed with chronic pain, even after adjusting for potential confounding variables. The risk of overdose was found to vary across different exposure groups. Specifically, individuals currently using gabapentin had a 61% increased risk of overdose (adjusted HR [95% CI] 1.61 [1.40 - 1.86]), while those using pregabalin had a 57% increased risk (adjusted HR [95% CI] 1.57 [1.37 - 1.81]). Additionally, individuals who switched between gabapentin and pregabalin had a 64% increased risk of overdose (adjusted HR [95% CI] 1.64 [1.37 - 1.97]).

The sensitivity analysis in this study demonstrated that the risk of overdose, as indicated by the HR, varied with different exposure periods. Specifically, the HR for users of both

gabapentin and pregabalin increased with a 90-day exposure period and decreased with a 30-day period. Notably, in both exposure group, the HR increased irrespective of whether the exposure period was set to 90 or 30 days. These findings underscore the importance of medication exposure duration in assessing overdose risk and suggest the need for revising clinical guidelines on prescription duration and monitoring. Furthermore, the CI became narrower when the 30-day exposure period was used among the three exposure groups. This change might be attributable to different assumptions or a stricter definition used in the sensitivity analysis. For example, altering the definition of exposure or outcome, or using different inclusion criteria, can lead to a more specific subset of data, potentially resulting in a narrower CI.

5.4.2 Comparison with other studies

The findings of this study indicated that the majority of overdose cases were recorded in the HES database, aligning with the study by Thomas et al. (2013), which validated records of suicide and self-harm in the CPRD and HES databases. Specifically, Thomas et al. (2013) found that 31.6% of self-harm cases, including drug overdose or poisoning, were not recorded in the CPRD database, with the majority (68.4%) documented within the HES database.

The risk of overdose associated with gabapentinoid use has been inconsistently studied due to variations in definitions, methodologies, and confounding adjustments. The within-individual design of this study enabled indication-specific confounding adjustments. The research revealed increased overdose risk in individuals using pregabalin, gabapentin, or both. Notably, individuals who switched between PGB and GBP, or vice versa, exhibited the highest HR (1.64), compared to those using only PGB or GBP. A parallel population-

based cohort study using Swedish registries also identified a similar relationship between gabapentinoid (time-varying exposure) use and adverse events, including unintentional overdoses (Molero et al., 2019). This study reported an increased incidence of accidental overdoses among gabapentinoid users compared to non-users, with HRs of 1.24 (95% CI: 1.19 to 1.28) for those using both medications, and 1.25 (95% CI: 1.20 to 1.30) for pregabalin users. However, gabapentin usage showed no significant association with unintentional overdose (Molero et al., 2019).

Another open cohort study utilised data from Swedish national registries administered by the Swedish National Board of Health and Welfare (NBHW) to examine pregabalin prescriptions and overdose-related mortality (Abrahamsson et al., 2017). Pregabalin was associated with overdose-related fatalities, with a HR of 2.82 (95% CI: 1.79–4.43) (Abrahamsson et al., 2017). In contrast, Macleod et al. (2019) investigated the risk of drug-related poisoning mortality in opioid-agonist-treated patients who were co-prescribed gabapentinoids using the CPRD and ONS databases. They found no connection between gabapentinoid co-prescription and drug-related poisoning mortality ($p = 0.373$). Both Abrahamsson (2017) and Macleod et al. (2019) focused on opioid-dependent patients on OMT, which may differ from the current study's cohort of chronic pain patients. Therefore, this demographic difference should be considered when comparing or interpreting the results.

In the study, several characteristics were identified as potentially increasing the risk of overdose. These include being middle-aged, female, having a history of SUD, and being concurrently prescribed both opioids and gabapentinoids. The ONS mortality reports (ONS, 2021b) indicate that middle-aged individuals in England and Wales experienced

the highest rates of drug poisoning deaths between 1993 and 2020. Drug misuse-related mortality was most prominent among those aged 45–49 years in 2020, closely followed by the 40–44 age group (ONS, 2021b). However, according to various studies, gabapentinoid poisoning is more likely to occur in the 18-30 age group than in any other (Boden et al., 2013; Molero et al., 2019).

The gender discrepancies in gabapentinoid misuse statistics are inconsistent. Chiappini and Schifano (2016) reported that gabapentinoid abuse, misuse, and dependency were more prevalent in women than in men according to the European database. Specifically, gabapentin use was found to be more common among female patients (Smith et al., 2015). However, multiple studies have indicated that a higher proportion of men tested positive for gabapentin and experienced drug overdoses (Slavova et al., 2018b; Gahr et al., 2013). In cases of gabapentinoid overdose, several studies have noted a history of substance use disorder and the concurrent use of opioids among individuals (Asomaning et al., 2016; Alblooshi et al., 2016; McNamara et al., 2015; Evoy et al., 2017).

5.4.3 Strength and limitation

This study focused on a prevalent adverse outcome, overdose, which significantly impacts individuals receiving treatment, the healthcare system, and the broader community. The study boasts several notable strengths. Firstly, it utilised both primary and secondary care data sources, employing code lists to identify the maximum number of overdose cases, a method previously used by other researchers in published studies. Other strengths include a large population-based cohort of more than 78,700 patients prescribed gabapentinoids for chronic pain, coupled with a lengthy follow-up time of eight years to assess the association between gabapentinoid use and overdose.

Additionally, the employment of a within-individual design effectively mitigated the influence of time-invariant confounding variables and thoroughly addressed residual confounding factors, such as those arising from individual genetics or family history. The methods used to determine medication usage and overdose in this research were extracted from the CPRD and HES databases. Medication use was based on prescriptions with specific product codes, while overdose cases were identified using appropriate Read and ICD-10 codes. This approach ensured the validity and completeness of the data on medication exposure and overdose cases, as well as the elimination of potential sources of bias, such as recall bias when medication usage and/or overdose are self-reported.

Possible limitations of this study include not accounting for lifestyle factors such as smoking and alcohol consumption, which may have led to an overestimation of overdose risk. Nevertheless, a previous occurrence of SUDs, specifically involving alcohol, cigarettes, and other drugs, was identified. Consequently, appropriate adjustments were made in the analysis to account for these potential confounding factors. The results of this study are align with those of previous studies, suggesting that the estimations were not significantly influenced by current lifestyle covariates.

Furthermore, there is limited information available regarding treatment adherence, a challenge also prevalent in clinical trials. To address this, patients who had only a single prescription were excluded from the study. The current research did not include cases of overdose presented to emergency departments, as data on such incidents were not accessible. This study covers patients who sought medical attention from general practitioners or those with severe overdose cases requiring hospitalisation. Therefore, it

is conceivable that the estimation of overdose cases might not be entirely accurate, as there could be both under- and over-estimation due to the absence of recorded overdose incidents in emergency department visits.

Another limitation of the current study was the natural limitations inherent in secondary databases for pharmacoepidemiology studies. Utilising HES-linked practice data restricted the study population to English practices, reducing the number of included patients by around 60% and potentially impacting the study's external validity. However, HES-linked data is essential for capturing differences in demographic and clinical features between primary and secondary care records. Moreover, it provides comprehensive and accurate estimates of outcomes.

5.5 Conclusion

The current study quantified the risk associated with the use of gabapentinoids and their potential for overdose. It identified an association between the current use of gabapentinoids and the risk of overdose, regardless of the exposure level. After adjusting for potential confounders, individuals' currently using gabapentin had a 61% increased risk of overdose compared to periods of non-use. Similarly, those currently using pregabalin had a 57% increased risk. Moreover, individuals prescribed both gabapentinoid medications (switching between pregabalin and gabapentin) had a 64% higher risk than during non-exposed periods.

Furthermore, this study has demonstrated the benefits of using record linkage to enhance the sensitivity of overdose identification. Analysis of patient data from the CPRD-HES linkage revealed that HES records accounted for approximately 71.3% of the total overdose events observed among patients during the study period. However, 13.5% of overdose cases were exclusively documented in the CPRD data. The study highlighted the importance of linking CPRD-HES data to identify overdose cases, rather than relying solely on CPRD data. These findings have significant implications for practice, as the substantial association with the current use of gabapentinoids has not generally been explored or quantified previously in patients with chronic pain.

Chapter 6 Association between gabapentinoid use and all-cause mortality in patients with chronic pain

6.1 Introduction

Chapter 5 demonstrated a significant association between gabapentinoid use and overdose risk during the exposure period compared to the non-exposure period. This increase in drug overdose might lead to increased risks of morbidity such as respiratory depression or long-term neurological damage and drug-related fatalities (Bradley, 2016; Tambon et al., 2021). Comparative international studies on gabapentinoid use and all-cause mortality are limited and often rely on post-mortem toxicological screening. Comprehensive data on all-cause deaths, drug-related poisoning deaths, and risk factors among gabapentinoid users are rare. This study addressed the knowledge gap by determining the proportion of all-cause mortality attributable to drug-related deaths involving gabapentinoid use in chronic pain patients.

6.2 Aim and objectives

This chapter aimed to examine the association between the use of gabapentinoids and all-cause deaths in UK primary care data, with linkage to ONS death certificates for further safety evaluation of gabapentinoid use. The objectives of this chapter included:

(1) Determining the proportion of patients with death records recorded within the CPRD, ONS, or both databases.
(2) Describing the demographics and clinical characteristics of gabapentinoid users with all-cause mortality.
(3) Evaluating the association between current exposure to gabapentinoid drugs and all-cause death, in comparison to individuals not currently exposed to these medications.

More details about the method are described in Chapter 2, Section 2.2.4.

6.3 Results

6.3.1 ONS-linked population

The number of patients eligible for linkage to the ONS death certificate database, the number of patients who were prescribed each drug, and the characteristics of the study cohort were presented in the previous chapter (Chapter 5: Section 5.4.1 and Table 5-1).

6.3.2 Number and proportion of death cases in CPRD, ONS, or both

Out of the total linked patients (n = 78,787), 12,751 (representing 16.2%) had records of death recorded within the study period. Within this group, 84 patients (0.1%) had a death record only in CPRD (group 1), and 6,563 patients (8.3%) had a death record only in ONS data (group 2). There were 6,104 patients (7.7%) with records in both databases (group 3), and 66,036 (83.8%) were censored observations (group 4). The process of identifying each of the four groups is summarised in Figure 6-1.

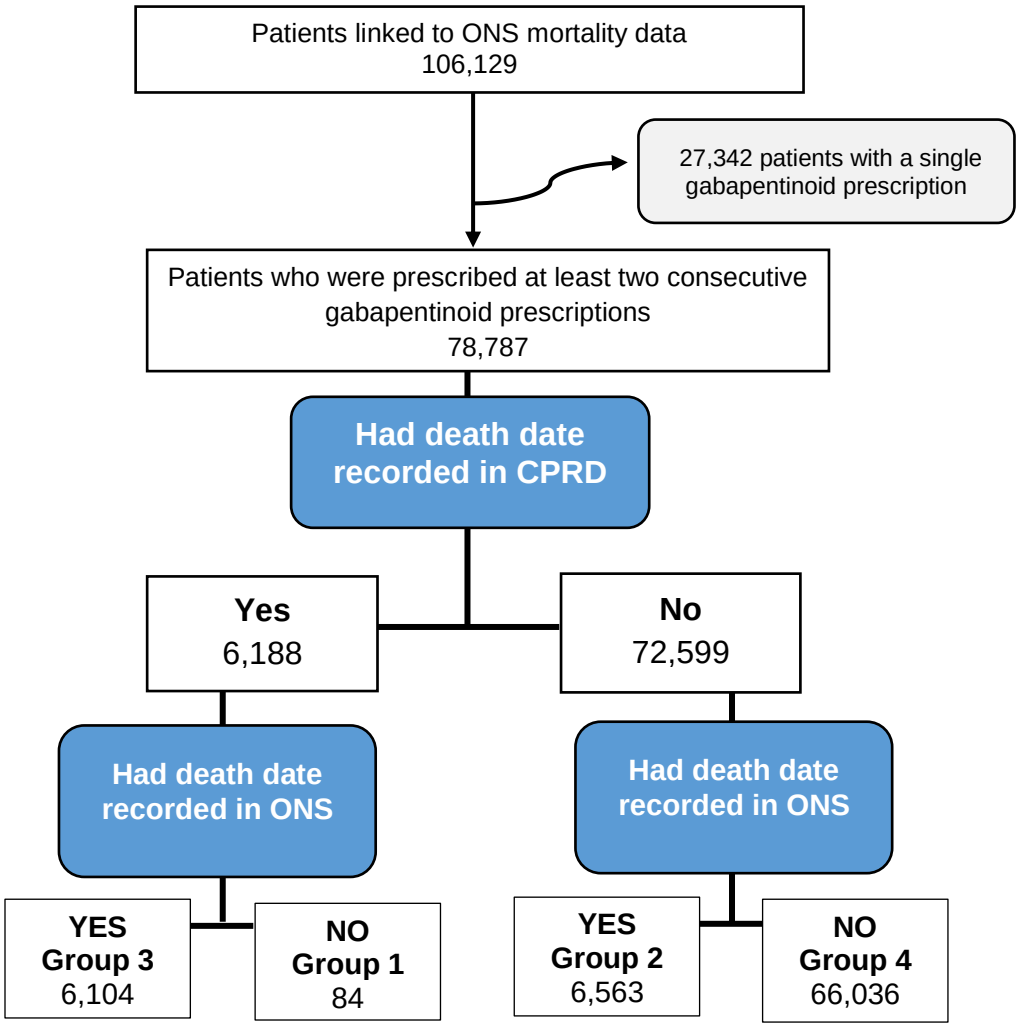


Figure 6-1: Flow Diagram Outlining the Process of Patient Group Identification According to the Existence of Death Date

6.3.3 Comparison of dates of death recording in both databases (CPRD – ONS)

The records of patients who had death records in both the CPRD and ONS databases were analysed further to estimate the time gap between the two death dates (Table 6-1). Of the 6,104 death records, 4,679 patients (76.7%) had their deaths recorded on the same day in both databases. In contrast, 1,370 patients (22.4%) had their deaths

documented with a delay of up to 30 days between the two recorded dates, not including those recorded on the same date. A delay of more than one month was observed in 55 patients (0.9%). The death records of 1,223 individuals (20.04%) were initially documented in ONS data, with a median delay of 4 days (IQR 1, 12) before being recorded in the GP system. For those whose death records were initially recorded in primary care (n = 202 (3.3%)), there was a median gap of 1 day (IQR 1, 13) between the recording of death dates in primary care and ONS data (Table 6-1).

Table 6-1: Time Gap between Death Recording Dates in CPRD and ONS Datasets, Gap Category, and Number of Patients in Each Database

Time gap category (days of the gap in recording between CPRD and ONS)	**Number of patients with a record of death in both datasets N= 6,104**
No gap (same recording date in CPRD and ONS)	4,679 (76.7%)
Very short gap (≤ 2 days)	587 (9.6%)
Short gap (>2 days and ≤7days)	293 (4.8%)
Intermediate gap (>7 days and ≤14 days)	268 (4.4%)
Long gap (> 14 days and ≤30 days)	222 (3.6%)
Prolong gap 1 (>30 and ≤60 days)	24 (0.4%)
Prolong gap 2 (>60 and ≤90 days)	1 (0.0%)
Prolong gap 3 (>90 days)	30 (0.5%)
Dataset first recorded	**Number of Patients with a Record of death in both datasets N= 6,104**
The number of deaths first recorded in ONS	1,223 (20.04%)
Number of deaths first recorded in CPRD	202 (3.3%)

CPRD: Clinical Practice Research Datalink; ONS: Office for National Statistics

6.3.4 Follow up time

Table 6-2 shows the median follow-up days for each exposure group. The patients who used pregabalin, or those who switched between pregabalin and gabapentin (both exposure group), had the longest follow-up periods. Their median follow-up was 2229 days (6.1 years) (IQR: 1019–2874 days, equivalent to 2.8 to 7.9 years) and 2226 days (6.1 years) (IQR: 1500–2717 days), respectively (Table 6-2).

Table 6-2: Follow-Up Days (Years) by Exposure Group

Exposure group	Median Days of Follow-up (yrs.)	IQR (25%, 75%) (yrs.)
Gabapentin	2118 (5.8)	1244-2754 (3.4 – 7.5)
Pregabalin	2229 (6.1)	1019-2874 (2.8 - 7.9)
Both	2226 (6.1)	1500-2717 (4.1 – 7.4)

IQR: interquartile range

6.3.5 Number and proportion of all-causes mortality events

During the follow-up, 12,751 (16.2%) patients from the linked population (n = 78,787) died. The number of patients who died in each exposure treatment group is presented in Table 6-3. The proportion of patients with a recorded death during the study period varied across exposure groups, ranging from 11.2% in users of both drugs to 18.5% in pregabalin users (Table 6-3). The number of death events in the exposed and non-exposed periods is detailed in Table 6-4. Of these death cases, a higher number of all-cause deaths occurred within the gabapentin group during the exposed period, with 2,644 deaths (37.95%) compared to other exposed periods among the exposure groups (Table 6-4).

Table 6-3: Number (%) of Patients Who Died by Exposure Group

Event	Gabapentin group N=41,707 (%)	Pregabalin group N=22,310 (%)	Both group N=14,770 (%)
Patients who died during the study period	6,967 (16.7%)	4,124 (18.5%)	1,660 (11.2%)

Table 6-4: Number (%) of All-Cause Mortality Events by Exposure Periods

Event	Gabapentin group N= 6,967	Pregabalin group N= 4,124	Both group N=1,660
All-cause mortality events in exposed periods	2,644 (37.95%)	1,805 (43.8%)	575 (34.6%)
All-cause mortality events in non-exposed periods	4,323 (62.05%)	2,319 (56.2%)	1,085 (65.4%)

The patients who did not die during the study were censored at the earliest of the following dates: leaving the practice (the transfer-out date), or the study end date. The end of the study period was the most common reason for censored observations across the three exposure groups (Table 6-5).

Table 6-5: The Cause and Number of Censored Patients by Exposure Group

Cause of censoring	Gabapentin group N= 34,740 (%)	Pregabalin group N=18,186 (%)	Both group N=13,110 (%)
Transfer out	3,716 (10.7%)	2,202 (12.1%)	1,202 (9.2%)
End of the study	31,024 (89.3%)	15,984 (87.9%)	11,908 (90.8%)

6.3.6 Characteristics of patients who died among CPRD-ONS linked population

Of the 12,751 cases of all-cause mortality, females constituted the majority in the study population across the three exposure groups: 3,921 (56.3%) in the gabapentin group, 2,412 (58.5%) in the pregabalin group, and 977 (58.9%) in both exposure group. The majority of deaths occurred among those aged between 71 and 80 years (n = 552, 33.3%) in both exposure group and in those over 80 years in the gabapentin and pregabalin exposure groups (34.8% and 34%, respectively). The IMD category for patients who died varied across the three groups: 1,530 (22%) patients were in the middle deprivation category with a score of 3 in the gabapentin group, 910 (22.1%) in the least deprived category for pregabalin, and 349 (21%) in the most deprived category for both group. One year prior to gabapentinoid initiation, 592 (8.5%), 323 (7.8%), and 112 (6.7%) patients had been diagnosed with cardiovascular disease in the gabapentin, pregabalin, and both exposure groups, respectively. The majority of patients had no comorbidities (74.9%). A history of SUD was diagnosed in 440 (3.5%) patients one year before gabapentinoid initiation. Gabapentin had the highest proportion of patients with a history of overdose one year before their death event (n = 95, 1.36%) across the exposure groups. Additionally, 3,091 (49.1%) and 1,696 (44.6%) patients with all-cause mortality events in the gabapentin and pregabalin groups, respectively, were co-prescribed opioids. However, antidepressants were the most commonly co-prescribed medications in both exposure group (Tables 6-6).

Table 6-6: Demographic and Clinical Characteristics of Patients Who Died Among the CPRD-ONS-Linked Population (N=12,751)

Patient Characteristics	Gabapentin n=6,967 (%)	Pregabalin n= 4,124 (%)	Both n=1,660 (%)
Gender [a]			
Male	3,046 (43.7%)	1,712 (41.5%)	683 (41.1%)
Female	3,921 (56.3%)	2,412 (58.5%)	977 (58.9%)
Age in years at baseline*			
Median (IQR)	76 (66 – 83)	75 (65 – 83)	74 (64 – 81)
Range	19 -106	18 - 105	24 - 99
Age rank			
18-30	25 (0.4%)	36 (0.9%)	18 (1.1%)
31-40	85 (1.2%)	89 (2.2%)	40 (2.4%)
41-50	287 (4.1%)	223 (5.4%)	103 (6.2%)
51-60	636 (9.1%)	437 (10.6%)	159 (9.6%)
61-70	1,372 (19.7%)	781 (18.9%)	347 (20.9%)
71-80	2,141 (30.7%)	1,154 (28%)	552 (33.3%)
>80	2,421 (34.8%)	1,404 (34%)	441 (26.6%)
IMD score (% from total)			
Missing	9 (0.1%)	2 (0.05%)	2 (0.12 %)
1 (least deprived)	1,350 (19.4%)	910 (22.1%)	333 (20.1%)
2	1,416 (20.3%)	828 (20.1%)	322 (19.4%)
3	1,530 (22%)	861 (20.9%)	336 (20.2%)
4	1,346 (19.3%)	737 (17.9%)	318 (19.2%)
5 (most deprived)	1,316 (18.9%)	786 (19.1%)	349 (21%)
Comorbidities at baseline [b]			
No comorbidity	5,223 (75%)	2967 (71.9%)	1,271 (76.6%)
Cardiovascular disease	592 (8.5%)	323 (7.8%)	112 (6.7%)
Diabetes	215 (3.1%)	145 (3.5%)	53 (3.2%)
COPD	389 (5.6%)	218 (5.3%)	93 (5.6%)
Stroke	295 (4.2%)	201 (4.9%)	54 (3.3%)
Anxiety	78 (1.1%)	115 (2.8%)	25 (1.5%)
Depression	175 (2.5%)	155 (3.8%)	52 (3.1%)

Patient Characteristics	Gabapentin n=6,967 (%)	Pregabalin n= 4,124 (%)	Both n=1,660 (%)
Other characteristics at baseline			
Patients with SUD [c]	198 (2.8%)	179 (4.3%)	63 (3.8%)
Overdose [e]	95 (1.36%)	77 (1.87%)	34 (2.05%)
Using death risk increasing drugs [d]			
benzodiazepines	368 (5.9%)	267 (7.02%)	108 (6.5%)
Opioids	3,091 (49.1%)	1,696 (44.6%)	687 (41.4%)
z-drugs	336 (5.3%)	256 (6.7%)	116 (7%)
Antidepressant	2,496 (39.7%)	1,586 (41.7%)	703 2.4%)

COPD– Chronic obstructive pulmonary disease; IMD – index of multiple deprivations; IQR – interquartile range; SUD – substance use disorder
*Calculated at the start of gabapentinoid treatment;
a- One patient was indeterminate regarding gender type;
b- Comorbidity was within 1 year before the start of gabapentinoid treatments;
c- History of substance use disorder within one year before the start of gabapentinoid prescription
d- Death risk increasing drugs at least one prescription of these drugs within 1 year before starting gabapentinoid treatment.
e- History of overdose one year before death.

6.3.7 The cause of death

The causes of death for the participants who experienced the event are summarised in Table 6-7. The majority of the deaths were from non-drug-related causes [gabapentin: 6,810 (97.8%), pregabalin: 3,991 (96.8%), and both: 1,597 (96.2%)]. A small number of deaths had unknown causes across the three exposure groups. Drug-related deaths were highest among pregabalin users, at 103 (2.5%) (Table 6-7). Additionally, of the 232 DRDs, 73 (31.5%) involved a gabapentinoid.

Table 6- 7: Number (%) of Death Events by Cause of Death and by Exposure Groups

Cause of death	Gabapentin group N= 6,967	Pregabalin group N=4,124	Both group N=1,660
Unknown-cause of deaths	64 (0.9%)	30 (0.7%)	27 (1.6%)
All-cause deaths*	6,810 (97.8%)	3,991 (96.8%)	1,597 (96.2%)
Drug-related deaths	93 (1.3%)	103 (2.5%)	36 (2.2%)

*The all-cause deaths do not include drug-related death

6.3.8 Cox proportional regression is defined as a time-varying exposure

The findings of the primary analysis, which used a Cox proportional hazards model to investigate the association between gabapentinoid usage and all-cause mortality in chronic pain patients, are presented in the following section. This analysis included statistical testing of the proportional hazards assumption, graphical evaluation of the survival function, and statistical testing for the equality of the survival functions. These preliminary steps were completed prior to the primary analysis. The association between gabapentinoid usage and all-cause mortality is initially reported as unadjusted HRs with 95% CIs, followed by the adjusted HRs (95% CIs) derived from the final multivariable analysis.

6.3.8.1 Graphical assessment of survivor function

The KM curves for survival functions were generated for each exposure group (Figures 6-2, 6-3, and 6-4). There was a violation of the proportional hazards assumption in the gabapentin and pregabalin exposure groups, while no violation was observed in the group with both exposure.

6.3.8.1.1 Gabapentin exposure group

The KM curve for survival functions shows a crossover between the two periods at one point (175 days) (Figure 6-2). The global test for the proportional hazards assumption (chi-squared = 63.46) was statistically significant (P < 0.001), indicating a violation of the PH assumption. Consequently, the analysis periods were divided into two intervals: 0–175 days (0–0.5 years) and 175–2921 days (0.5–8 years).

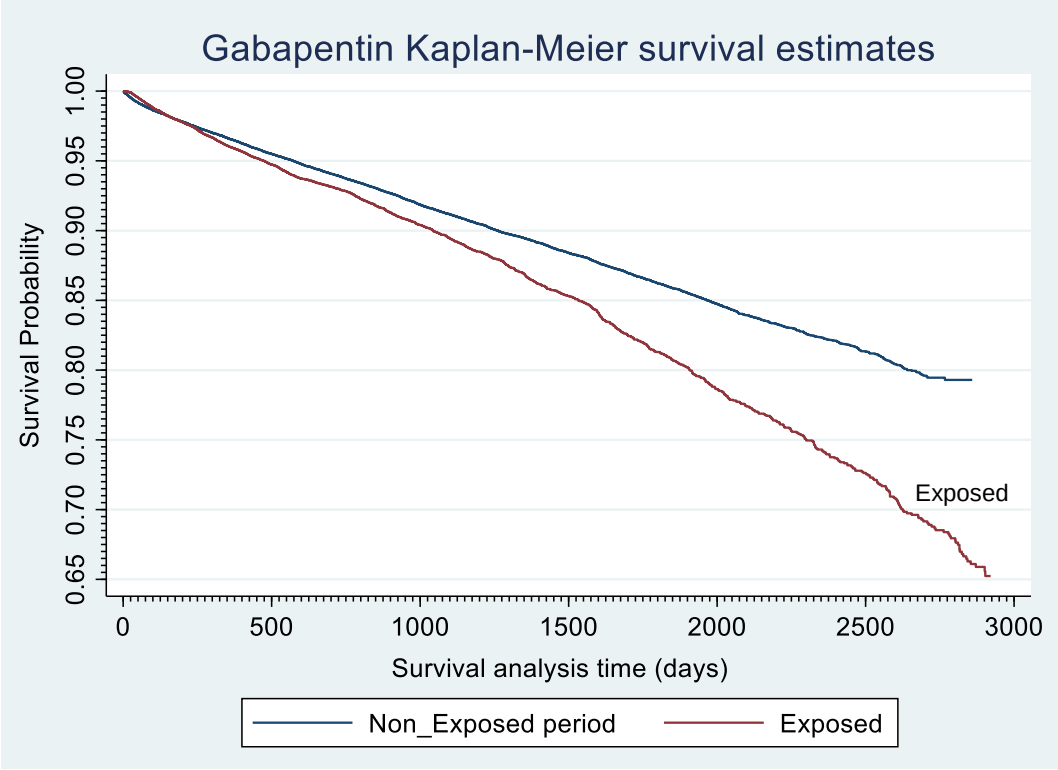


Figure 6-2: Kaplan Meier Survival Estimates for Exposed and Non-Exposed Periods within the Gabapentin Exposure Group

6.3.8.1.2 Pregabalin exposure group

The KM curve for survival functions shows a crossover between the two periods at one point (150 days) (Figure 6-3). The global test for the proportional hazards assumption (chi-squared = 20.60) was statistically significant (P < 0.001), indicating a violation of the

PH assumption. Consequently, the analysis periods were divided into two intervals: 0–150 days (0–0.4 years) and 150–2921 days (0.4–8 years).

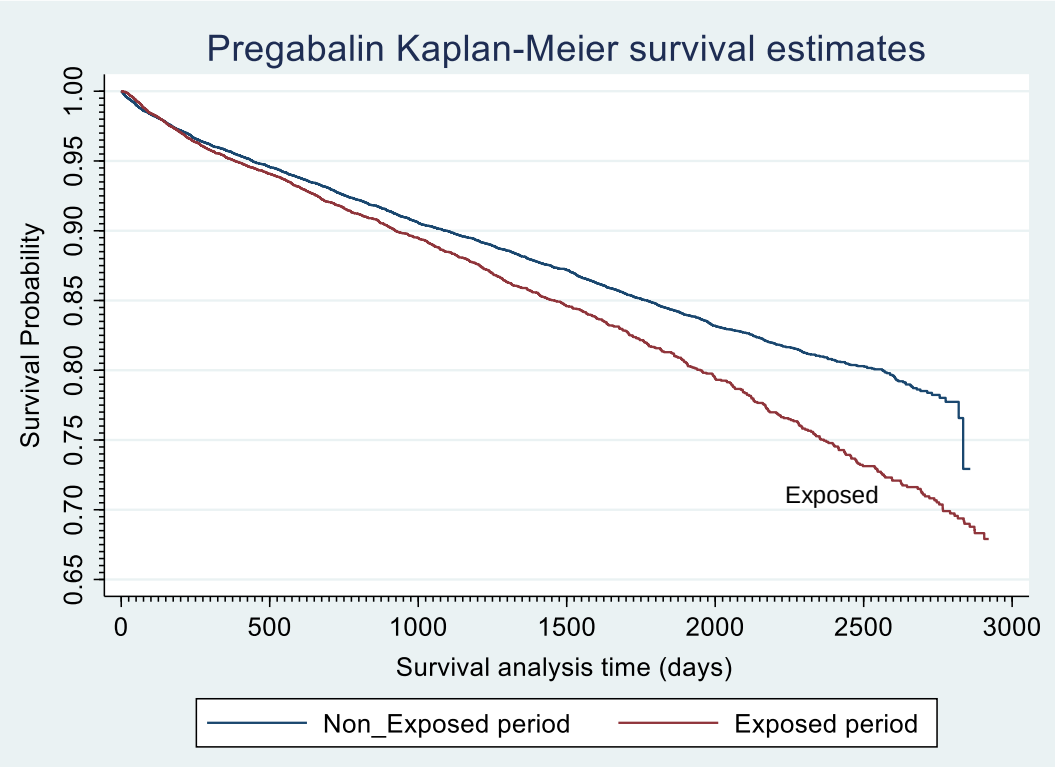


Figure 6-3: Kaplan Meier Survival Estimates for Exposed and Non-Exposed Periods within the Pregabalin Exposure Group

6.3.8.1.3 Both exposure group

The KM curve for survival functions is presented in Figure 6-4. These plots demonstrate that all-cause mortality was higher during exposed periods compared to non-exposed periods for users in both exposure group.

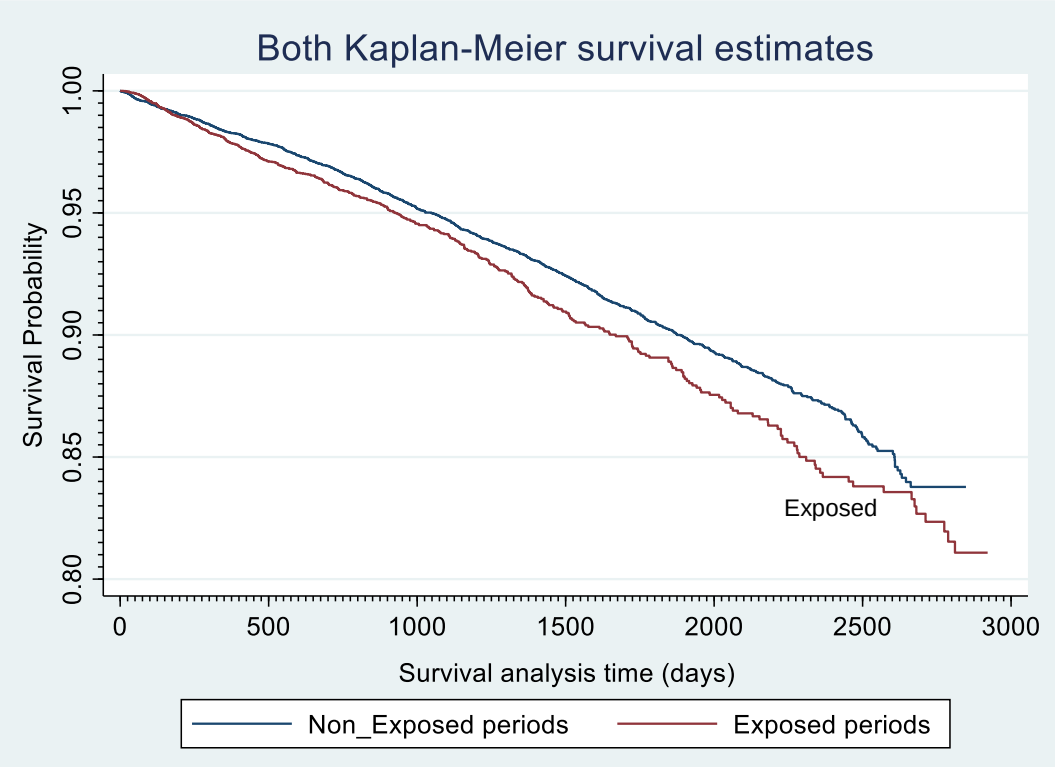


Figure 6-4: Kaplan Meier Survival Estimates for Exposed and Non-Exposed Periods within Both Exposure Group

6.3.8.2 Statistical assessment of the equality of survivor function

The results of the log-rank test, employed for the statistical evaluation of the equality of survival functions, reveal a statistically significant difference ($p < 0.001$) in survival (occurrence of death) between the exposed and non-exposed periods. Consequently, the null hypothesis must be rejected for each of the three exposure groups (gabapentin, pregabalin, and both)

6.3.8.3 Cox proportional hazards regression

A separate model was applied to each exposure group, with the respective unadjusted HRs and 95% CIs presented in this section. The unadjusted HRs indicated a significant association between gabapentinoid use (across the three exposure groups) and all-cause

mortality. The unadjusted HR for gabapentin use and all-cause deaths was the highest among the exposure groups, at 1.43 (95% CI 1.35–1.51, p < 0.001). This suggests a 43% increase in the risk of mortality during exposed periods compared to non-exposed periods (Table 6-8).

Table 6-8: Current Use of Gabapentinoid and the All-Cause Mortality

Exposure group	HR-Unadjusted	95% CI
Non-exposure	Reference	-
Gabapentin	1.43	(1.35 - 1.51)
Pregabalin	1.29	(1.20 - 1.38)
Both	1.17	(1.05 - 1.29)

HR: hazard ratio; CI: confidence interval

6.3.8.3.1 Proportionality of hazards assumption

The global test (Schoenfeld residuals test) for the proportional hazards assumption for the gabapentin and pregabalin exposure groups yielded chi-squared values of 63.46 and 20.60, respectively, with statistically significant p-values (P < 0.001) for both of them. Consequently, the proportional hazards assumption was violated for these groups. However, the global test for the proportional hazards assumption for the both exposure group resulted in a chi-squared value of 0.19, which was not statistically significant (P-value = 0.6659). Therefore, there is no evidence to reject the hypothesis of proportional hazards for both exposure group.

6.3.8.3.2 Effect of confounders on the risk for all-cause mortality

A change in the HR was observed when each potential confounder (age, gender, deprivation score, history of SUD, medications that may increase the risk of mortality, and comorbidities) was introduced independently and sequentially, one at a time, into the Cox

regression model. The impact of the covariates on the HR differed across the three exposure groups. While the change in HR varied with different confounders, age appeared to have a significant effect (a ±10% change in the HR) in both the gabapentin and pregabalin exposure groups. Therefore, age was included along with other a priori confounders in the final fully adjusted model (Table 6-9).

Table 6-9: The Results of Univariate Analysis Presented the Effect of Potential Confounders on Unadjusted Hazard Ratios for All Cause of Mortality by Exposure Groups

Covariate	Gabapentin HR (95% CI)	Pregabalin HR (95% CI)	Both HR (95% CI)
HR Unadjusted (95% CI)	1.43 (1.35 - 1.51)	1.29 (1.20 - 1.38)	1.17 (1.05 - 1.29)
Priori confounders (PC)*	1.40 (1.32 - 1.48)	1.28 (1.19 - 1.37)	1.15 (1.04 - 1.29)
Gender + PC	1.43 (1.35 - 1.51)	1.28 (1.20 - 1.38)	1.16 (1.05 - 1.29)
Age at the start of the treatment + PC	1.22 (1.15 - 1.29)	1.14 (1.06 - 1.23)	1.24 (1.12 - 1.38)
IMD score + PC	1.44 (1.36 - 1.52)	1.29 (1.20 - 1.38)	1.17 (1.06 - 1.30)
SUD + PC	1.42 (1.34 - 1.51)	1.28 (1.19 - 1.37)	1.16 (1.05 -1.29)

* Priori confounders include comorbidity and the use of medications that may increase mortality. CI: Confidence interval; HR: Hazard ratio; IMD: index of multiple deprivation; PC: Priori confounders; SUD: substance use disorder

6.3.8.3.3 Final adjusted model

Using gabapentinoids was significantly associated with an increased risk of all-cause mortality. The adjusted HRs and 95% CIs for all-cause mortality with each covariate are presented in Table 6-10. The HRs for the risk of all-cause mortality in all exposure groups changed after controlling for covariates. The HR values for all exposure groups decreased following adjustments, with a 24% reduction in the adjusted HR for gabapentin compared to the unadjusted, a 17% decrease in the adjusted HR for the pregabalin exposure group,

and a 2% decrease in the adjusted HR for the both exposure group. However, the risk of all-cause mortality associated with current gabapentinoid use remained high compared to non-use across all exposure groups (Table 6-10).

Table 6-10: Multivariable Analysis Results Presented the Unadjusted and Adjusted Hazard Ratios by Exposure Groups

Exposure group	Unadjusted	Adjusted
	HR (95% CI)	HR (95% CI)
Non-exposure	1.0 (Reference)	1.0 (Reference)
Gabapentin[a]	1.43 (1.35 - 1.51)	1.19 (1.13 - 1.27)
Pregabalin[b]	1.29 (1.20 - 1.38)	1.12 (1.04 - 1.20)
Both[c]	1.17 (1.05 - 1.29)	1.15 (1.04 - 1.29)

a Adjusted for age, concomitant use of other increasing risk drugs, comorbidity
b Adjusted for age, concomitant use of other increasing risk drugs, comorbidity
c Adjusted for concomitant use of other increasing risk drugs, comorbidity
CI: Confidence interval; HR: Hazard ratio

When the end of the exposed periods was defined as 90 days after the last gabapentinoid prescription within these periods, the use of these prescriptions remained significantly associated with the risk of all-cause mortality. However, no association was observed between gabapentinoid use and the risk of all-cause mortality when the duration of the exposed periods was defined as ending 30 days after the last gabapentinoid prescription (Table 6-11).

Table 6-11: Sensitivity Analyses: the Associations between Gabapentinoid Treatment and Risk of All-Cause Mortality by Exposure Groups and Different Definitions of Exposed Period

	Adjusted
Exposure group	**HR (95% CI)**
Non-exposure	1.0
Exposure periods of 90days after the last collected prescription (60+90)	
Gabapentin[a]	1.26 (1.21 - 1.33)
Pregabalin[b]	1.18 (1.11 - 1.26)
Both[c]	1.21 (1.10 - 1.35)
Exposure periods of 30 days after the last collected prescription (60+30)	
Gabapentin[a]	0.74 (0.70 - 0.78)
Pregabalin[b]	0.73 (0.68 - 0.78)
Both[c]	0.78 (0.70 - 0.88)

CI: Confidence interval; HR: Hazard ratio
a Adjusted for age, concomitant use of other increasing risk drugs, comorbidity
b Adjusted for age, concomitant use of other increasing risk drugs, comorbidity
c Adjusted for concomitant use of other increasing risk drugs, comorbidity

6.4 Discussion

6.4.1 Main findings

This study explored death events recorded within the CPRD, the ONS, and both databases for patients diagnosed with chronic pain who were prescribed pregabalin and gabapentin. The number of death events in the study population (CPRD-ONS linked) was 12,751, representing 16.2% of the total linked patients (n = 78,787). Over half of the deaths were recorded within the ONS database, 6,563 (51.5%), while 6,104 (48.2%) were identified in both the CPRD and ONS databases. Less than 0.5% of the death cases were identified solely within CPRD (n = 84), with no corresponding dates indicated within the ONS database. Among those with death records in both databases, death dates matched exactly in 76.7% of cases. A delay of up to a month was identified in 22.4% of the death events, while 0.5% had a discrepancy of more than 90 days between the dates. CPRD was, on average, 4 days later than the ONS death date (median 4 days, interquartile range (IQR) 1–12), and there was only a 1-day average difference when the CPRD death date was recorded earlier than ONS (median 1 day, IQR 1–13).

Several reasons could explain the delayed recording of deaths in GP practices. Delays often arise from the need for post-mortem examinations, inquests, or coroner referrals, particularly in cases of unclear, violent, suspicious, or unnatural deaths, such as those resulting from accidents, neglect, suicide, or occurring in specific circumstances like during operations or in custody (Woods and Cooke, 2021). Additionally, certain causes of death, like heart failure or suicide, may not always occur in hospitals. This, along with varying documentation practices for different causes of death, might lead to discrepancies in recording times between ONS and CPRD (Hollingworth et al., 2016).

In the UK, deaths must be registered within 5 days, but delays can occur, especially in unexpected or suspicious cases requiring a post-mortem examination. While there is a legal requirement for prompt death registration to ensure accurate national records (considered the 'gold standard' by ONS), this requirement does not extend to primary care records. In GP practices, the recording of death dates serves clinical and administrative purposes, such as avoiding distress to families or for audit reasons (Woods and Cooke, 2021; Singh, 2013). GP records often reflect the date the practice is informed of the death, which may be later than the actual date, especially if the GP didn't certify the death. This trend contributes to GP-recorded dates generally being later than ONS dates. Incorrect information supplied to GPs is possible but not the primary cause of these discrepancies (Gallagher et al., 2019; Woods and Cooke, 2021).

Most deaths were associated with the gabapentin exposure group (n = 6,967, 54.6%) compared to other exposure groups (pregabalin and both). Among the 12,751 deaths, there were 232 (1.8%) DRDs identified across the three exposure groups, with 73 (31.5%) deaths related to gabapentinoids. The characteristics associated with all-cause death included older age, female gender, cardiovascular disease, and being co-prescribed opioids. However, the IMD category for deceased patients varied across the three exposure groups, with the most deprived category in the both exposure group, the minor category for pregabalin, and the middle category for gabapentin. A small proportion of patients had a history of SUD (3.5%) among those with death events. In addition, 206 (1.6%) patients had a history of overdose one year before death, with gabapentin having the highest proportion of overdose (n = 95, 46.1%). Opioids (40%) and antidepressants (37.5%) were the most co-prescribed medications one year before the initiation of

gabapentinoid. Approximately 5% of the patients were prescribed benzodiazepines or Z-drugs. Only 1,041 patients, accounting for 8% of the total, died during the study without using any other medication alongside gabapentinoid.

This population-based cohort study estimated the risk of all-cause mortality associated with current exposure to different gabapentinoid groups (pregabalin, gabapentin, and both), adjusting for potential confounding variables. The risk of death from all causes was elevated among all studied gabapentinoid exposure groups during current exposure periods compared to periods of no use (non-exposed periods). The risk of all-cause mortality was highest in the gabapentin exposure group, with approximately a one-fifth increase in the all-cause mortality risk during exposed periods [HR (95% CI): 1.19 (1.13–1.27)]. Compared to non-exposed periods, the risk of all-cause mortality was 15% greater during exposed periods in the both exposure group [HR (95% CI): 1.15 (1.04–1.29)]. In comparison with the other exposure groups, pregabalin had the lowest risk of all-cause mortality. The risk of all-cause mortality for pregabalin during exposed periods was 12% higher compared to non-exposed periods [HR (95% CI): 1.12 (1.04–1.20)].

The sensitivity analysis results found that when the end of the periods during which gabapentinoid prescriptions were taken was defined as 90 days after the last prescription, there was a significant association between the usage of these prescriptions and the risk of all-cause death. However, no discernible link was found between the use of gabapentinoids and the likelihood of death from any cause when considering the length of the periods in which the medication was used up to 30 days following the last prescription. This indicates that the association between drug use and mortality is highly dependent on how the exposure period is defined. Furthermore, it implies that the timing,

duration, or how the drug was used is crucial in determining its impact on mortality. In addition, the change in results might indicate that other factors, not accounted for in the main analysis, could influence the association. For example, the health status of patients, other medications they are taking, or their adherence to the drug regimen could play a role.

6.4.2 Comparison with other studies

This study identified discrepancies between CPRD primary care records and ONS national data in death dates for about a quarter of cases, though 76.7% of the death dates matched in both databases (ONS-CPRD). This is consistent with Harshfield et al. (2020), who found a 76.8% match in death dates between UK primary care and national records. In this study, death date in CPRD was later than ONS in 20.04% of cases, and in 3.3% of cases, it was the other way around. Harshfield et al. (2017) also noted that in 3% of cases, death date in CPRD was a week earlier than ONS. Gallagher et al. (2019) found that in one-fifth of cases, the GP practice recorded a later death date than the ONS official death certificate.

In this study, 0.1% (84 cases) of death records were found in the CPRD database but not in the ONS, possibly because ONS data only covers deaths in England and Wales, not other UK regions (Woods and Cooke, 2021). On average, CPRD death dates were 4 days later than those in ONS, with a median difference of 4 days (IQR 1-12). When CPRD recorded deaths earlier, the average gap was 1 day, which aligns with Harshfield et al. (2017) who found that CPRD GOLD's death dates were, on average, later by a median of 5 days (IQR 1-15).

The current study found an association between gabapentinoid use and an increased risk of all-cause mortality, with gabapentin exposure accounting for 54.6% (6,967 cases) of deaths and a 20% higher risk of death during exposure. However, making comparisons with previous studies is challenging due to differences in design and practices. A Swedish study showed a higher risk of suicidal behavior and deaths associated with gabapentinoids (adjusted HR 1.26). In Scotland, gabapentinoids, particularly gabapentin, were increasingly implicated in DRDs (Torrance et al., 2020). Kalk et al. (2022) reported a rise in gabapentinoid-related deaths in England, increasing from 8.9% in 2014 to 32.3% in 2020. In this analysis, 1.8% (232 cases) of the 12,751 deaths examined were drug-related, with 31.5% involving gabapentinoids, aligning with the Tayside drug death database, which showed 39% of DRDs linked to gabapentinoids (Torrance et al., 2020).

Associated risks with gabapentinoid-related all-cause mortality include older age, female gender, substance abuse, cardiovascular disease, and opioid co-prescription. A study found 104 gabapentin-related deaths, with 62.5% being female (Tharp et al., 2019). Another study indicated significantly higher age-standardized all-cause mortality among gabapentinoid users in NHS Tayside and NHS Fife in 2016, with a risk ratio of 2.16 (Torrance et al., 2020). In this chapter the common pre-existing conditions in deceased gabapentinoid users included cardiovascular disease and COPD. In Australia, gabapentinoid toxicity deaths often involved cardiomegaly, emphysema, nephrosclerosis, and severe hepatic steatosis as primary pre-existing conditions (Darke et al., 2022).

The findings of this chapter indicate a high rate of drug co-prescription among individuals who died during the study period. Over 40% of these individuals were co-prescribed opioids, and 37.5% were on antidepressants in the year before death. These findings

align with a study in Australia (2000-2020) that found other drugs involved in all gabapentinoid-related toxicity deaths, such as antidepressants, hypnotics, and opioids, each contributing 90.1%, 76.9%, and 60.5% to deaths (Darke et al., 2022). A post-mortem study found that non-heroin opioids and antidepressants were frequently detected with gabapentinoids in blood samples (Nahar et al., 2019), with significant percentages of gabapentin and pregabalin cases combined with opiates and antidepressants. Kalk et al. (2022) also noted that 25.3% of gabapentinoid-related deaths in England involved opioids.

In this study, a small percentage (3.5%) of patients prescribed gabapentinoids who died during the study period had a SUD. Drug use disorder (DUD) and DRDs are closely linked to health inequality. Research has shown that combining opioids with gabapentin or pregabalin in individuals with substance use issues can significantly increase the risk of acute overdose fatalities (Kalk et al., 2022; Kriikku and Ojanpera, 2021; Lyndon et al., 2017; Nahar et al., 2019). Risk factors for problematic drug use are multifaceted, often stemming from social, economic, and health factors, rather than just personal choice (Bonell and Fletcher, 2008). In England's most economically deprived areas, drug use disorder is a leading cause of disease. Addressing this issue is crucial to reduce adverse outcomes, including overdose deaths (GOV.UK, 2021a).

6.4.3 Strength and limitation

This is the first study in England to utilise and confirm official and reliable death records to identify the number of fatalities and the association between gabapentinoid use and all-cause mortality in patients with a chronic pain diagnosis. In contrast to previous studies that identified gabapentinoid-related deaths based on post-mortem toxicological

screening, this study used a population-based cohort design to link the CPRD-ONS population for an 8-year follow-up period. This research may compensate for time-invariant factors and more effectively address unobserved confounders by employing a within-individual design, such as confounding by indication.

This research has certain limitations. Because the ONS death certificates were only linked to patients registered in practices in England, all-cause fatalities, including DRDs, could not be documented or recognised in other UK nations. Furthermore, there might be a possible selection bias due to differences between gabapentinoid users eligible for linkage data and those who are not. However, recent research found similarities in demographics and medication prescribing across practices, both with and without CPRD linkage eligibility, in a previous studies (Gallagher et al., 2019).

While the CPRD is the UK's most comprehensive healthcare record and the ONS registers all-cause mortality in England and Wales, only some practices agreed to link CPRD with ONS death certificates, limiting the research to a subset of all-cause deaths in England and Wales.

Furthermore, due to the time lag between ONS registration and database inclusion, the number of fatalities and DRDs within the years was underestimated. Patients eligible for linkage to the ONS data source and who had been followed up since 2012 were promptly reduced by 33.5% out of the total non-linked sample of 316,347. Researchers must consider the trade-off between the loss of patient numbers and the knowledge gained from the linked data. Nevertheless, it's worth noting that linked ONS data has been utilised in some CPRD GOLD studies to provide additional information on the cause of death,

which would otherwise be lacking in primary care (Glover et al., 2017; Ratib et al., 2015; Wing et al., 2016).

6.5 Conclusion

This research indicated that most death records were documented in the ONS database, with 76.7% of death date events matching exactly among patients with a death record in both databases using the CPRD-ONS linked data. Gabapentinoid use was associated with a higher risk of all-cause death, including DRDs. These associations differed across the three exposure groups, with gabapentin showing the most significant risk of all-cause death compared to the other exposures. However, the results of the sensitivity analysis indicate that no association was found when using a different definition of exposure time period (30 days). This result raises questions about the nature of the drug's impact on mortality and suggests a need for further research to understand the conditions under which the drug might be associated with increased mortality.

Older age, female gender, patients with SUDs, and patients who were co-prescribed additional drugs (especially opioids) were identified as the most common demographics and characteristics among patients who died during the study. Prescriptions for older adults and those with drug use problems, as well as co-prescribing other medications that raise the risk of mortality, may need to be reviewed. The government should form a task group to encourage initiatives aimed at improving health outcomes for people who misuse drugs, and practitioners should exercise caution when combining gabapentinoids with other prescriptions like opioids, particularly in chronic pain patients.

Chapter 7 General discussion and implications

The key results of the thesis are presented in this chapter, followed by a discussion analysing the overall strengths and weaknesses of the thesis. The chapter further includes dedicated sections discussing the potential applications of the findings in clinical practice, their impact on policy-making, and their effect on future research. Finally, a comprehensive conclusion is provided.

7.1 Main findings

Chapter 3 examined a 16-year trend (2005-2020) in pregabalin and gabapentin prescribing for CNCP patients in primary care. It found a significant increase in gabapentinoid prescriptions per 1000 registrants, with a 7.8-fold rise and days' supply growing by 31.8% for gabapentin and 169% for pregabalin. There was an overall increase in the incidence and prevalence of gabapentinoids per 10,000 CPRD registrants throughout the study period. Over half of the initial prescriptions were for unlicensed indications, primarily chronic back pain, while nearly 20% were for licensed indications. The average prescribed daily dose for both drugs consistently increased.

Chapter 4 analysed the effects of gabapentinoid reclassification on prescribing trends and doses over eight years using ITS analysis. The reclassification led to an 18% reduction in gabapentin and a 13% reduction in pregabalin monthly prevalence. The baseline trend before and immediately after reclassification remained unchanged, indicating a minimal immediate impact on prevalence rates.

Chapter 5 investigated the association between gabapentinoid use and overdose risk in CNCP patients, accounting for confounders and comparing data from CPRD and HES. Discrepancies were found between the databases, with 13.5% of overdoses recorded only in CPRD and 71.2% only in HES. Gabapentinoid use was associated with substantial overdose risks (61% for gabapentin, 57% for pregabalin, and 64% for both). Overdose risks were higher among individuals from deprived areas (31.3%) and those with a history of SUD (18.6%). Many overdoses involved patients also prescribed antidepressants and opioids, suggesting interactions or independent overdose risks. Comorbidities like depression and anxiety were prevalent among those who overdosed.

Finally, chapter 6 explored the association between gabapentinoid use and all-cause mortality, including drug-related deaths, using time-varying exposure analysis. It found discrepancies in death date recording between CPRD and ONS in nearly a quarter of cases, but 76.7% of death dates matched. Pregabalin, gabapentin, or both were associated with increased all-cause mortality (HR values of 1.12, 1.19, and 1.15, respectively). Of the total mortalities, 1.8% were DRDs, with 31.5% of these being gabapentinoid-related. Older age, female gender, SUD, cardiovascular disease, and co-prescription of opioids were common among those who died. Additionally, over 40% of patients were co-prescribed opioids, 37.5% antidepressants, and about 5% benzodiazepines or z-drugs.

7.2 Methodological approaches in the thesis: strength and limitation

The research expanded knowledge of gabapentinoid use in CNCP patients by examining medication use for different pain conditions and the impact of reclassifying gabapentinoids as controlled drugs. It identified factors linking their use to overdose and mortality risks, including DRDs. These findings should be interpreted cautiously, considering the study's methodology and analysis limitations.

One of the strengths of this research is the utilisation of CPRD data, a large primary care database in the UK, the research's findings are externally valid and potentially generalisable to other countries with similar health systems. Comprehensive prescribing records enabled reliable medication exposure analyses through various designs, detailing annual prescribing prevalence and incidence, as well as PDD over 16 years. This long-term approach reduced variability risks associated with shorter timeframes.

The research used an ITS design to evaluate changes in gabapentinoid prevalence and dosing before and after policy implementation, detecting delayed or intermittent changes and comparing pre- and post-intervention trends. A cohort study design investigated the association between gabapentinoid use and overdose or death risk using prospectively recorded data to avoid recall bias. A within-subject design mitigated individual variance and adjusted for time-invariant covariates, addressing unobserved confounding variables more effectively.

HES-linked population data examined the association between gabapentinoid use and overdose risk over eight years. Most overdoses were documented in HES, with 13.5%

recorded only in CPRD due to varying overdose severities. Using both databases enhanced the study's robustness and inference. Half of the death events recorded in the ONS database, with 48% in both databases, and less than 0.5% recorded only in CPRD, provided a comprehensive view of drug exposure effects and death causes, with CPRD's reported death dates consistent with ONS records (Gallagher et al., 2019).

Using time-varying analysis mitigated immortal time bias, enabling more robust conclusions about the association between gabapentinoid use and overdose or fatality risk and highlighting the importance of using appropriate methods to reduce potential bias in epidemiological research (Agarwal et al., 2018).

This research had several limitations. The challenge of managing chronic pain without specific medications required individualised treatments identified through EHR diagnosis codes, which may lead to misclassification bias. Chronic pain identification relied on Read and medical codes in CPRD records, potentially categorising symptoms rather than actual diagnoses. Conditions like RA and OA may be underestimated or delayed in diagnosis (Jordan et al., 2010).

Chronic pain reporting in CPRD can be skewed towards severe conditions like MI or stroke unless pain is the primary complaint (Kadam et al., 2013). The QOF excludes most chronic pain conditions, potentially underestimating the number of UK primary care chronic pain patients using gabapentinoids (NHS, 2022b; Yu et al., 2017). The research assumes strict adherence to prescribed regimens, potentially overestimating medication use since up to 50% of patients may not follow long-term treatments accurately (Burkhart and Sabaté, 2003). Drugs administered in secondary care, emergency departments, or drug abuse treatment centres, as well as over-the-counter, illegal, and diverted

pharmaceuticals, are not recorded in CPRD (Baker et al., 2015; Taylor et al., 2014). However, this likely doesn't significantly impact analgesic use data as chronic conditions are primarily managed by GPs in the UK.

Factors like pain intensity, gabapentinoid tolerability, comorbidity severity, and lifestyle measures were not included, potentially causing residual confounding and affecting the association between gabapentinoid use and overdose or fatality risk. Additionally, substance abuse and pain conditions in the UK primary care database are often not verified, leading to possible misclassification of patient characteristics.

7.3 Implications for clinical practice and policy

The results obtained from this study have numerous implications that may be examined for prospective implementation or adoption into practice.

7.3.1 Implications of findings from prescribing trends for chronic pain management

Prescription trends show an overall increase in gabapentinoid use for chronic pain, especially for unlicensed indications like back and musculoskeletal joint pain, necessitating continuous monitoring. Only one-fifth of these prescriptions were for licensed indications. The rise in gabapentinoid prescriptions carries significant risks, including side effects, misuse, and dependency. Although effective for neuropathic pain, gabapentinoids have abuse potential and are linked to increased overdose deaths, particularly when used with opioids (Peckham et al., 2018c). The rise in gabapentinoid prescriptions for chronic pain has significant implications for healthcare providers and policymakers.

Healthcare professionals must balance the risks and benefits of gabapentinoids, assess their effectiveness, monitor outcomes, and follow standardised protocols to protect patient health. Enhancing patient education on proper use and risks is crucial. Clinicians should consider alternative pain treatments, including non-pharmacological options like mindfulness, behavioural therapy, movement-based therapies, and other pharmacological alternatives, as these have proven effective for chronic pain (NICE, 2021b; Kolber et al., 2021). When gabapentinoid prescriptions rise, optimising educational and lifestyle strategies advised by NICE is essential (NICE, 2021b). This

ensures proper medication use, reduces the risk of misuse and side effects, offers alternative pain management approaches, and prevents dependency issues. Patient involvement in decision-making ensures alignment with their preferences, needs, and risk profiles (NICE, 2021b). Following NICE guidelines promotes evidence-based practices, improving overall patient care and safety.

Regulatory bodies have reclassified gabapentinoids, imposing stricter prescribing and dispensing controls in response to their harms (DEA, 2005; GOV.UK, 2018; Blackmer et al., 2019). This reclassification necessitates a re-evaluation and tightening of prescribing guidelines to ensure gabapentinoids are recommended only when necessary and following a comprehensive risk-benefit analysis. Furthermore, the development or enhancement of robust monitoring systems is essential to track prescribing trends and associated adverse outcomes, facilitating the early identification of potential issues. It is imperative to implement balanced policies that prevent misuse while ensuring that patients who genuinely benefit from gabapentinoids can access them without undue barriers.

7.3.2 Implications of the findings from gabapentinoid reclassification into controlled drugs

This study was the first to assess the impact of gabapentinoid reclassification on the prevalence of gabapentinoid users among chronic pain patients. Contrary to expectations, the study found no significant immediate change in the monthly prevalence of gabapentin or pregabalin users' post-reclassification, though there was a slight change

in trend (Chapter 4). Mahase et al. (2020) predicted that reclassification would decrease usage by making these medications harder to prescribe, dispense, and collect.

The reclassification of gabapentinoids has broad implications for healthcare providers, patients, and the healthcare system. It has influenced prescribing patterns, leading to increased caution and the use of alternative treatments. Healthcare providers now face additional responsibilities and constraints, including stricter legal and regulatory requirements for prescribing and monitoring controlled substances. Pharmacies must adhere to stringent storage, dispensing, and record-keeping practices (GOV.UK, 2018), and pharmacists need to counsel patients about the reclassification and its implications.

Patients may experience changes in pain management strategies, requiring education and support for transitioning to alternative treatments. Stricter regulations could create access barriers, necessitating more frequent healthcare visits, which can be challenging for those with mobility issues or in remote areas.

The limited options for managing chronic pain place considerable pressure on prescribers. Many GPs and medical organisations support the reclassification but also urge the government to enhance support services for patients dependent on medication and seeking to discontinue its use. The lack of alternative therapies poses difficulties for patients without access to psychiatric support, physiotherapy, or other specialised services.

7.3.3 Implications of findings of the association between gabapentinoid use and the risk of overdose and all-cause mortality

This thesis identifies a significant association between gabapentinoid use (gabapentin and pregabalin) and increased risks of overdose and all-cause mortality, with these drugs implicated in two-thirds of DRDs among chronic pain patients. This underscores the need for a comprehensive assessment of the benefits and risks of these medications, tailored to individual patient needs. Although gabapentinoids are often seen as safer alternatives to opioids (Goodman and Brett, 2017; Morrison et al., 2017), their potential for ADRs, abuse, and overdose risks, particularly when used with opioids, presents significant clinical concerns (Peckham et al., 2018b; Shanthanna et al., 2017).

The research found that patients experiencing overdose or death were often co-prescribed antidepressants and opioids, followed by benzodiazepines (Chapters 5 and 6). Combining gabapentinoids with these medications increases the likelihood of overdoses and fatalities (Evoy et al., 2019; Macleod et al., 2019; Peckham et al., 2018b; Torrance et al., 2020). Healthcare providers must exercise caution when co-prescribing these drugs and regularly evaluate patients, especially those at higher risk of misuse or overdose, including individuals with mental health issues or SUDs (Evoy et al., 2017).

Patients using gabapentinoids need education on the benefits and risks before starting treatment. Emphasising the likelihood of only partial pain relief and the potential for side effects is crucial. Regular medication reviews are necessary to assess effectiveness and

side effects, and patient involvement in decision-making is essential for effective care planning (NHS, 2021a).

In the UK, the risk of gabapentinoid misuse is recognised, with warnings documented in the product characteristics for both drugs (EMA, 2023a; 2023b). NICE has published guidelines on the safe use and management of controlled drugs, including gabapentinoids, and is developing further guidelines for managing dependence and withdrawal (NICE, 2022). These guidelines recommend careful monitoring for signs of abuse or dependence and educating patients on the dangers of combining CNS depressants with their medication (NICE, 2022).

Healthcare providers should be aware of the limitations of current GP systems in identifying medication misuse risks and the need for integrated treatment strategies. In England, the National Drug Treatment Monitoring System (NDTMS) holds data on adults treated for drug or alcohol issues, but it cannot be linked with GP clinical systems, leaving primary care physicians without validated information on patients' SUD history (GOV.UK, 2017; PHE, 2018). Medicines management pharmacists play a critical role in managing patients with chronic pain, focusing on medication reviews and advising on safer alternatives. Emphasising education for practitioners and patients on the risks of gabapentinoids, particularly when used with other high-risk drugs, is vital. Developing a systematic framework for clinical decision-making and evidence-based guidelines for managing gabapentinoid misuse or abuse is also essential.

7.4 Implications for research

Future research is needed to validate these results and analyse the link between gabapentinoid use and overdose risk using other datasets, such as the A&E HES database. The impact of varying dosage levels and durations of exposure on adverse outcomes in patients using gabapentinoids for unlicensed conditions should also be investigated. Additionally, developing risk prediction models to individualise the risk of gabapentinoid abuse or misuse is crucial for identifying and monitoring high-risk individuals. These models should consider factors such as comorbidities, SUD history, and concurrent use of other analgesics.

This study evaluated the short-term impacts of gabapentinoid reclassification on prescribing and dosing patterns, but the long-term effects on drug misuse, deaths, and use of other high-risk medications remain unknown. Further research is needed to assess the long-term impacts and related harms of gabapentinoid reclassification.

There is a lack of information on the characteristics of individuals who continuously use other categories of pain-relieving medications, such as gabapentinoids, which have the potential to induce dependence. More research is required to identify signs of misuse or abuse among gabapentinoid users and to understand healthcare providers' perspectives on their use and diversion. This will contribute to promoting safer use and improving treatment planning.

Further studies are needed to explore the attitudes and knowledge of individuals who misuse gabapentinoids to achieve early prevention of related harms. Gabapentinoid use should be investigated in high-risk patients, such as those with SUDs. Additional

qualitative research is necessary to understand patients' feelings about the necessity of continuous gabapentinoid use, the frequency of adverse effects, and reasons for abuse or misuse. This will help enhance treatment strategies and address the issues related to gabapentinoid use.

7.5 Conclusion

This thesis highlights significant implications for chronic pain management with gabapentinoids. The increase in gabapentinoid prescriptions, especially for unlicensed uses, necessitates continuous monitoring due to risks of side effects, misuse, and dependency. Healthcare providers must balance these risks with benefits, incorporating patient education and alternative pain management strategies.

The reclassification of gabapentinoids as controlled drugs imposes stricter prescribing and dispensing practices, complicating patient access and pain management. Support services and alternative therapies are needed for those affected by these changes.

The research shows a strong association between gabapentinoid use and increased risks of overdose and all-cause mortality, particularly when combined with other high-risk medications. Comprehensive patient education, regular medication reviews, and cautious co-prescribing are essential. Developing risk prediction models and integrated treatment strategies is crucial for identifying and monitoring high-risk individuals.

Future research should validate these findings with diverse datasets, explore the long-term effects of reclassification, and understand the characteristics and perspectives of users and healthcare providers. This will contribute to safer use and better treatment planning for gabapentinoids.

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Appendices

Appendix I: ISAC Protocol

ISAC evaluation of protocols for research involving CPRD data

General information	
Protocol reference Id **20_000149**	
Study title **Trends of gabapentinoid prescribing associated overdose and mortality in chronic pain patients and the impact of gabapentinoid classification as a controlled drug**	
Research Area **Drug Safety** **Drug Utilisation** **Pharmacoepidemiology**	
Does this protocol describe an observational study using purely CPRD data? **Yes**	
Does this protocol involve requesting any additional information from GPs, or contact with patients? **No**	
Research team	
Role	Chief Investigator
Title	Associate Professor in Clinical Pharmacy Practice
Full name	Roger Knaggs
Affiliation/organisation	University of Nottingham
Email	Roger.knaggs@nottingham.ac.uk
Will this person be analysing the data?	No
Status	Confirmed
Role	Corresponding Applicant
Title	PhD
Full name	Joud Al-Friah
Affiliation/organisation	University of Nottingham
Email	Joud.alfriah@nottingham.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed
Role	Collaborator
Title	Associate Professor
Full name	Sonia Gran
Affiliation/organisation	University of Nottingham
Email	sonia.gran@nottingham.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Collaborator
Title	Associate Professor
Full name	John Williams
Affiliation/organisation	University of Nottingham
Email	John.williams7@nottingham.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Access to Data

Sponsor
University of Nottingham

Funding source for the study
Is the funding source for the study the same as Chief Investigator's affiliation?
Yes
Funding source for the study
University of Nottingham

Institution conducting the research
Is the institution conducting the research the same as Chief Investigator's affiliation?
Yes
Institution conducting the research
University of Nottingham

Method to access the data
Indicate the method that will be used to access the data
Institutional multi-study licence
Is the institution the same as Chief Investigator's affiliation?
Yes
Institution name
University of Nottingham

Extraction by CPRD
Will the dataset be extracted by CPRD
No

Multiple data delivery
This study requires multiple data extractions over its lifespan
No
Number of repeated data extractions required over the lifespan of this study

Date of ISAC feedback (date of approval)
21st January 2021

Appendix II: List of Indicative Medcode for Chronic Pain Diagnosis

Medcode	Term	Medcode	Term
Neuropathic pain			
321	Periodic migrainous neuralgia	**35117**	Spinal stenosis NOS
537	Facet joint syndrome	**35465**	Hereditary motor and sensory neuropathy type II
1254	Sciatic nerve lesion	**35537**	[X] Polyneuropathy, unspecified
1598	Post-herpetic neuralgia	**35785**	Chronic painful diabetic neuropathy
2284	Neuralgia unspecified	**37315**	Diabetic mononeuropathy
2342	Diabetic neuropathy	**38401**	Hereditary peripheral neuropathy NOS
2679	Lumbosacral neuritis; unspecified	**39528**	Hereditary peripheral neuropathy
2790	Peripheral neuropathy	**39692**	Polyneuropathy in herpes zoster
2925	Alcoholic polyneuropathy	**39858**	[X]Inflammatory polyneuropathy, unspecified
3370	Spinal stenosis	**41147**	Spinal stenosis of unspecified region
3958	Polyneuropathy	**41652**	Other toxic or inflammatory neuropathy
5002	Diabetic polyneuropathy	**41716**	Insulin dependent diabetes mellitus with polyneuropathy
5840	Acute back pain with sciatica	**43577**	Degenerative lumbar spinal stenosis
6055	Ischaemic optic neuropathy	**44095**	Polyneuropathy in disseminated lupus erythematosus
6884	Morton's neuralgia	**44512**	Idiopathic progressive polyneuropathy
6908	Other idiopathic peripheral neuropathy NOS	**45081**	Toxic neuropathy
7331	Ramsey - Hunt syndrome	**45467**	Non-insulin dependent diabetes mellitus with polyneuropathy
7635	Hereditary sensory neuropathy	**46301**	Type 1 diabetes mellitus with polyneuropathy
7795	Diabetes mellitus with neuropathy	**47409**	Type II diabetes mellitus with polyneuropathy
8591	Peripheral neuropathy - hereditary or idiopathic	**47465**	Polyneuropathy in polyarteritis nodosa
8823	Prolapsed lumbar intervertebral disc with sciatica	**48078**	Acute painful diabetic neuropathy
9912	Lumbar spinal stenosis	**49664**	Idiopathic peripheral autonomic neuropathy NOS
10223	Postherpetic neuralgia	**50099**	Peripheral autonomic neuropathy due to disease NOS
10722	Inflammatory and toxic neuropathy	**50527**	Type II diabetes mellitus with polyneuropathy
11544	Neuropathic pain	**50813**	Type II diabetes mellitus with mononeuropathy
11663	Neuropathic diabetic ulcer - foot	**52089**	Polyneuropathy in diphtheria
14740	Thoracic neuritis; unspecified	**54124**	Other toxic agent polyneuropathy
14866	Lumbago with sciatica	**54992**	Neuralgia, neuritis and radiculitis unspecified

Medcode	Term	Medcode	Term
Neuropathic pain			
14883	Hereditary or idiopathic peripheral neuropathy NOS	**56272**	Polyneuropathy in disease EC
14884	Other idiopathic peripheral neuropathy	**56910**	Hereditary motor and sensory neuropathy type I
15331	Spinal stenosis; excluding cervical region	**57313**	Polyneuropathy in collagen vascular disease
15481	Toxic or inflammatory neuropathy NOS	**58758**	Polyneuropathy in porphyria
16368	Idiopathic peripheral autonomic neuropathy	**62401**	Polyneuropathy in rheumatoid arthritis
16397	Thoracic and lumbosacral neuritis	**62612**	Thoracic spinal stenosis
16491	Diabetes mellitus with polyneuropathy	**62674**	Type 2 diabetes mellitus with mononeuropathy
16884	Thoracic nerve root pain	**63555**	Polyneuropathy in disease NOS
17067	Autonomic neuropathy due to diabetes	**66241**	Closed injury sciatic nerve
17180	Postzoster neuralgia	**66336**	Polyneuropathy in amyloidosis
18075	Hereditary and idiopathic peripheral neuropathy	**67024**	Open injury sciatic nerve
18230	Type 1 diabetes mellitus with neuropathic arthropathy	**68105**	Type 1 diabetes mellitus with mononeuropathy
18425	Type 2 diabetes mellitus with polyneuropathy	**68960**	Polyneuropathy in hypoglycaemia
18492	Neuropathic foot blister	**71258**	Polyneuropathy in collagen vascular disease NOS
18534	Ulnar neuropathy	**72320**	Non-insulin dependent diabetes mellitus with mononeuropathy
23627	Thoracic and lumbosacral neuritis NOS	**72614**	Idiopathic lumbar spinal stenosis
23839	Neuralgia, neuritis or radiculitis NOS	**72889**	[X]Autonomic neuropathy/endocrine+metabolic diseases CE
24121	Intercostal neuropathy	**73730**	Degenerative thoracic spinal stenosis
24222	Polyneuropathy due to drugs	**93836**	Iatrogenic lumbar spinal stenosis
24226	Polyneuropathy unspecified	**95351**	Type II diabetes mellitus with mononeuropathy
24355	Polyneuropathy in vitamin B deficiency	**96256**	Axonal sensorimotor neuropathy
24571	Asymptomatic diabetic neuropathy	**97848**	Mumps polyneuropathy
24694	Insulin dependent diabetes mellitus with mononeuropathy	**97870**	Lumbar spinal stenosis secondary to other disease
27403	Geniculate herpes zoster	**98630**	Thoracic spinal stenosis secondary to other disease
27469	Sciatic hernia	**99231**	Type I diabetes mellitus with mononeuropathy
31551	Inflammatory polyneuropathy, unspecified	**100064**	Polyneuropathy in mumps
31709	Postherpetic polyneuropathy	**101311**	Insulin dependent diabetes mellitus with polyneuropathy

31790	Polyneuropathy in diabetes	**105825**	Familial amyloid polyneuropathy type III
Medcode	**Term**	**Medcode**	**Term**
Neuropathic pain			
32335	Geniculate ganglionitis	**106103**	Hereditary motor and sensory neuropathy type III
32527	Hereditary motor and sensory neuropathy	**106536**	Idiopathic thoracic spinal stenosis
33362	Horton's (histamine) neuralgia	**109760**	Diabetic peripheral neuropathic pain
34761	Sciatic nerve injury	**109865**	Type 2 diabetes mellitus with polyneuropathy
110363	[X]Polyneuropathy/other endocrine+metabolic diseases CE		
Back pain			
110567	[X]Polyneuropathy/other musculoskeletal disorders CE	**12862**	Ankylosis/instability of cervical;thoracic or lumbar spine
154	Low back pain	**15109**	Lumbalgia
409	Sacroiliac disorder	**17022**	Lumbosacral strain
557	Backache; unspecified	**17838**	Sacroiliac instability
1212	Coccygodynia	**18171**	Atlanto-axial instability
1335	Pain in lumbar spine	**19020**	O/E - lumbar pain on palpation
1606	Sacroiliac strain	**19395**	Referral to back pain clinic
1720	Lumbago	**20068**	Sacroiliac ankylosis
3324	Back pain without radiation NOS	**24796**	Back pain worse on sneezing
3763	C/O - low back pain	**25630**	O/E - abd. pain - L.lumbar
4680	Spasm of back muscles	**31344**	Cervical spine instability
4948	Pain in thoracic spine	**36558**	O/E - abd. pain - R.lumbar
5023	Acute back pain - lumbar	**38810**	Ankylosis of spine NOS
5476	Acute back pain - disc	**43684**	Thoraco-lumbar ankylosis
5899	C/O - lumbar pain	**49344**	Lumbosacral ankylosis
5916	Acute back pain - thoracic	**50723**	Sacral instability NOS
5923	Acute back pain - unspecified	**52079**	Sacral ankylosis NOS
5958	Back stiffness	**55486**	Lumbar spine ankylosis
6704	Back pain; unspecified	**55993**	Cervical spine ankylosis
8102	Lumbosacral instability	**59215**	Atlanto-axial ankylosis
9682	Referral to back pain clinic	**62664**	Thoracic spine ankylosis
10135	Hypermobility of the coccyx	**64853**	Thoracic spine instability
10231	Chronic low back pain	**67231**	Atlanto-occipital ankylosis
11998	Pain in coccyx	**89022**	Cervico-thoracic instability
12189	Mechanical low back pain	**98803**	Cervico-thoracic ankylosis
12598	Lumbar spine instability	**105661**	Low back pain clinical pathway
12669	Atlanto-occipital instability	**111836**	Simple sciatic hernia
Fibromyalgia			
717	Fibromyalgia	**4698**	Fibrositis of neck
1230	Scapulohumeral fibrositis	**33474**	Rheumatism and fibrositis unspecified
1807	Fibrositis arm	**35937**	Rheumatism or fibrositis NOS
2237	Fibrositis unspecified	**58543**	Nodular fibrositis of chronic rheumatic disease
4657	Fibromyalgia		
Headache and migraine pain			

129	Headache	**12017**	Sinus headache
Medcode	**Term**	**Medcode**	**Term**
Headache and migraine pain			
130	Frontal headache	**12511**	Ophthalmoplegic migraine
161	Migraine	**14700**	Migraine NOS
191	Tension headache	**16247**	Headache site
1197	[D]Headache	**17011**	Viral headache
1788	Occipital headache	**17762**	[D]Abdominal migraine
2424	Common migraine	**20932**	Aching headache
2554	Cluster headache	**21663**	Bilateral headache
2861	Abdominal migraine	**22685**	Status migrainosus
3220	Classical migraine	**23621**	Migraine variant NOS
3340	Temporal headache	**27930**	Complicated migraine
3658	Hemiplegic migraine	**28031**	Other forms of migraine
3716	Sinus headache	**28092**	Other forms of migraine NOS
4188	Headache - post traumatic	**29329**	[X]Psychogenic headache
4949	Morning headache	**41497**	Common migraine NOS
5029	H/O: migraine	**42903**	Shooting headache
5110	Vascular headache, not elsewhere classified	**53813**	[X]Other migraine
5335	Throbbing headache	**53833**	[X]Other specified headache syndromes
5509	Migraine variants	**65262**	Moebius' ophthalmoplegic migraine
5660	Sick headache	**83480**	History of headache
5767	C/O - a headache	**93476**	Referral to headache special interest general practitioner
6139	Chronic post-traumatic headache	**95330**	[X]Vascular headache, not elsewhere classified
6433	Abdominal migraine - symptom	**98205**	[X]Chronic headache disorder
7512	[X]Tension type headache	**98239**	[X]Cervicogenic headache
9004	Basilar migraine	**103451**	H/O migraine with aura
9048	Parietal headache	**103502**	Migraine with aura
9633	Atypical migraine	**103537**	Chronic tension-type headache
9891	Generalised headache	**103602**	Migraine without aura
9999	Muscular headache	**103755**	Frequent episodic tension-type headache
10583	Ophthalmic migraine	**103899**	Infrequent episodic tension-type headache
11138	Migraine - menstrual	**103916**	[X]Primary exertional headache
11321	Unilateral headache	**103973**	Migraine induced by oestrogen contraceptive
11389	Migraine prophylaxis	**103989**	[X]Primary cough headache
Musculoskeletal joint pain			
332	Prepatellar bursitis	**24958**	Localised; primary osteoarthritis of the wrist
396	Osteoarthritis	**25776**	Parr beak tear-post/med menisc
443	Knee joint effusion	**25793**	Localised; primary osteoarthritis of the ankle and foot
554	Knee joint pain	**27535**	Stiff knee NEC
639	Elbow osteoarthritis NOS	**27603**	Rheumatoid arthritis and other inflammatory polyarthropathy
658	Osteoarthritis NOS; of the hand	**27834**	Osteoarthritis NOS; of IP joint of toe

665	Knee osteoarthritis NOS	**27972**	Osteoarthritis NOS
Medcode	**Term**	**Medcode**	**Term**
Musculoskeletal joint pain			
829	Osteoarthritis spine	**28908**	Localised; primary osteoarthritis of toe
844	Rheumatoid arthritis	**29718**	Lateral meniscus derangem.NOS
1029	Rheumatism NOS - multiple	**29863**	Polyalgia
1296	Patellofemoral osteoarthritis	**30548**	Rheumatoid vasculitis
1312	Foot osteoarthritis NOS	**31054**	Rheumatoid arthritis - multiple joint
1408	Polymyalgia	**31200**	Localised osteoarthritis; unspecified; NOS
1418	Arthralgia of multiple joints	**31209**	Myopathy due to rheumatoid arthritis
1699	Meniscus derangement NEC	**31974**	Patellar tendon nontraum.rupt.
1959	Thumb osteoarthritis NOS	**32001**	Adult-onset Still's disease
2209	Hip osteoarthritis NOS	**32839**	Localised; primary osteoarthritis
2229	Osteoarthritis NOS; of acromioclavicular joint	**32891**	Localised; secondary osteoarthritis of other specified site
2487	Osteoarthritis NOS; of knee	**33445**	Oth. internal knee derangement
2692	Internal derangement of knee	**33479**	Localised; secondary osteoarthritis of the lower leg
2852	Knee arthritis NOS	**33574**	Localised; secondary osteoarthritis of the shoulder region
3057	Osteoarthritis and allied disorders	**34023**	Osteoarthritis NOS; of sacro-iliac joint
3147	Osteoarthritis NOS; of shoulder region	**34035**	Localised; secondary osteoarthritis of the ankle and foot
3309	Locked knee	**34095**	Horiz cleavage tear-med menisc
3317	Other intern.knee derang.NOS	**34122**	Localised osteoarthritis; unspecified
3677	Arthropathies NOS	**34804**	Localised osteoarthritis; unspecified; of the lower leg
3814	Osteoarthritis NOS; of sternoclavicular joint	**34806**	Localised; primary osteoarthritis of the forearm
4031	Bursitis of knee NOS	**34867**	Generalised osteoarthritis NOS
4309	Housemaids knee	**35150**	Other osteochondr dissec-knee
4353	Generalised osteoarthritis - OA	**35527**	Osteoarthritis NOS; of unspecified site
4461	Localised osteoarthritis; unspecified; of the ankle and foot	**35629**	Unsp.polyarthr.-multiple site
4464	Osteochondritis of knee	**35936**	Polyarthritis
4490	Finger osteoarthritis NOS	**36215**	Joint disord.NOS-multiple site
4578	Sero negative polyarthritis	**36327**	Generalised osteoarthritis of the hand
4604	H/O: knee problem	**37100**	Fibular collat.lig.bursitis
4878	Toe osteoarthritis NOS	**37431**	Rheumatoid arthropathy + visceral/systemic involvement NOS
4967	Osteoarthritis NOS; pelvic region/thigh	**38019**	Erosive osteoarthrosis
5299	Infrapatellar bursitis	**38471**	Other knee lig. old disruption
5776	Osteoarthritis NOS	**38516**	Miners' knee
5802	Osteoarthritis NOS; of shoulder	**38631**	Generalised osteoarthritis of unspecified site
6044	Arthralgia of knee	**38713**	Lateral menisc.post.horn deran
6133	Locking knee	**38750**	Radial tear of medial meniscus

6166	Anterior knee pain	**38821**	Other joint sympt.-multip.site
Medcode	**Term**	**Medcode**	**Term**
Musculoskeletal joint pain			
6355	Loose body in knee	**39303**	Lateral menisc.derang.unspecif
6812	Osteoarthritis NOS; of hip	**40972**	Osteoarthritis NOS; of subtalar joint
6887	Osteoarthritis NOS; of 1st MTP joint	**41088**	Localised; secondary osteoarthritis of the upper arm
6916	Seronegative rheumatoid arthritis	**41090**	Oligoarticular osteoarthritis; unspecified; of lower leg
6962	Old bucket handle tear-medial	**41378**	Osteoarthritis of cervical spine
7040	Disorder of patella unspecified	**41941**	Rheumatoid arthritis of PIP joint of finger
7392	Relapsing polychondritis	**41985**	Oligoarticular osteoarthritis; unspecified; other spec sites
7429	Osteoarthritis of spine	**42045**	Localised; secondary osteoarthritis
7688	Patellar tendinitis	**42299**	Rheumatoid arthritis of MCP joint
7866	Osteoarthritis NOS; of MCP joint	**42859**	Multiple tears-lat meniscus
8125	Old ant.cruciate lig.disrupt.	**44041**	Localised; secondary osteoarthritis of pelvic region/thigh
8202	Osteoarthritis NOS; of ankle	**44203**	Other rheumatoid arthritis of spine
8309	Musculoskeletal pain - joints	**44743**	Rheumatoid arthritis of cervical spine
8350	Flare of rheumatoid arthritis	**44948**	Lateral menisc.ant.horn derang
8406	Swollen knee	**45749**	Synov osteochondromat-knee
8680	Patellofemoral disorder	**45815**	Localised; secondary osteoarthritis of the forearm
9010	Osteoarthritis NOS; of lesser MTP joint	**46988**	Parr beak tear-post/lat menisc
9517	Knee pain	**47024**	Osteoarthritis of thoracic spine
9649	Osteoarthritis NOS; of wrist	**48214**	Oligoarticular osteoarthritis; unspec; of unspecified sites
9681	Osteoarthritis NOS; of DIP joint of finger	**48832**	Rheumatoid arthritis of wrist
9707	Seropositive errosive rheumatoid arthritis	**49067**	Rheumatoid arthritis of hip
9991	Old bucket handle tear-lat men	**49227**	Other rheumatoid arthropathy + visceral/systemic involvement
10389	Anterior knee pain	**49545**	Localised osteoarthritis; unspecified; of unspecified site
10695	Discoid lateral meniscus	**50848**	Osteoarthritis NOS; of the upper arm
11032	Osteoarthritis NOS; of PIP joint of finger	**50861**	[X]Inflammatory polyarthropathies
11569	Synovitis of knee	**50863**	Rheumatoid arthritis of knee
12019	Seropositive rheumatoid arthritis; unspecified	**51238**	Rheumatoid arthritis of 1st MTP joint
12440	Sinding-Larsen's dis.(patella)	**51239**	Rheumatoid arthritis of ankle
14939	Internal knee derangement NOS	**52095**	Oligoarticular osteoarthritis; unspecified; of shoulder
15052	Osteoarthritis NOS; other specified site	**52897**	Ankle osteoarthritis NOS
15060	Knee stiff	**52930**	Ankylosis of the knee joint
15144	Osteoarthritis NOS; of the lower leg	**52960**	[X]Other meniscus derangements
15206	Wrist osteoarthritis NOS	**52979**	Transient arthropathy-knee

15441	Localised osteoarthritis; unspecified; of shoulder region	**53184**	Osteoarthritis of spine NOS
Medcode	**Term**	**Medcode**	**Term**
Musculoskeletal joint pain			
15447	Osteoarthritis NOS; of ankle and foot	**53339**	Reactive arthropathy of knee
15839	Localised; primary osteoarthritis of the pelvic region/thigh	**53741**	[X]Other polyarthrosis
16242	Localised osteoarthritis; unspecified; of the hand	**53858**	Osteoarthritis of more than one site; unspecified; NOS
16345	Subpatellar bursitis	**53979**	Radial tear-lateral meniscus
16623	Tibial collateral lig.bursitis	**54224**	Localised; primary osteoarthritis of unspecified site
17092	Osteoarthritis cervical spine	**54225**	Crystal arthropathy NOS-knee
17176	Degen lesion artic cart knee	**54350**	Osteoarthritis NOS; of other tarsal joint
17230	Generalised arthritis	**54563**	Osteochondritis dissec-patella
17412	Rheumatoid arthrit. monitoring	**55143**	Horiz cleavage tear-lat menisc
17516	Old torn meniscus of knee	**55388**	Osteoarthritis NOS; of talonavicular joint
17554	Suprapatellar bursitis	**56063**	Old lat.collat.lig.disruption
17658	Effusion of knee	**56068**	[X]Oth intrnl derangemnts/knee
18112	Localised osteoarthritis; unspecified; of other spec site	**56202**	[X]Seropositive rheumatoid arthritis; unspecified
18155	Rheumatoid bursitis	**56244**	Old post.cruciate lig.disrupt.
18602	Localised; primary osteoarthritis of elbow	**56294**	[X]O spontn disrptn/lig(s)knee
18826	Osteoarthritis of spine	**56322**	Unspecified polyarthropathy
19197	Medial menisc.post.horn derang	**57267**	Oligoarticular osteoarthritis; unspecified; multiple sites
19713	Osteoarthritis NOS; of elbow	**57586**	Algodystrophy of knee
20204	Knee joint contracture	**57912**	Localised; secondary osteoarthritis NOS
20449	Multiple stiff joints	**59616**	Oligoarticular osteoarthritis; unspecified; of hand
20472	Localised; primary osteoarthritis of other specified site	**59637**	Localised osteoarthritis; unspecified; of the upper arm
20626	Localised osteoarthritis; unspecified; pelvic region/thigh	**59738**	Rheumatoid arthritis of elbow
20660	Localised; primary osteoarthritis NOS	**59836**	Flexion contracture-knee
20864	Old med.collat.lig.disruption	**60537**	Localised osteoarthritis; unspecified; of the forearm
20984	Lateral meniscus derangement	**62037**	Arthr assoc oth dis-knee
21001	Old tear of lateral meniscus	**62482**	Periph detach-medial meniscus
21159	Localised; primary osteoarthritis of the lower leg	**62752**	Multiple tears-medial meniscus
21350	Localised; primary osteoarthritis of the hand	**63198**	Rheumatoid arthritis of DIP joint of finger
21358	Rheumatoid arthritis of shoulder	**63365**	Rheumatoid arthritis of distal radio-ulnar joint
21528	Oligoarticular osteoarthritis; unspecified	**65727**	[X]Other disorders of patella

21635	Swan-neck finger deformity	**65748**	Osteoarthritis NOS; of distal radio-ulnar joint
Medcode	**Term**	**Medcode**	**Term**
Musculoskeletal joint pain			
21994	Iliotibial band syndrome	**67978**	Periph detach-lateral meniscus
22452	Osteoarthritis of lumbar spine	**68648**	Oligoarticular osteoarthritis; unspecified; of pelvis/thigh
23638	Localised; secondary osteoarthritis of the hand	**68712**	Localised; secondary osteoarthritis of unspecified site
23646	Primary generalized osteoarthrosis	**68848**	Old capsular knee lig.disrupt.
23676	Generalised osteoarthritis of multiple sites	**70221**	[X]Other specified rheumatoid arthritis
23819	Medial menisc.ant.horn derang.	**70425**	Osteoarthritis NOS; of tibio-fibular joint
23934	Arthropathy NOS of multiple sites	**70658**	Rheumatoid arthritis of talonavicular joint
24022	Localised; primary osteoarthritis of the shoulder region	**71784**	Rheumatoid arthritis of other tarsal joint
24148	Enthesopathy of knee	**72109**	Oligoarticular osteoarthritis; unspecified; of ankle/foot
24152	Osteoarthritis NOS; of the forearm	**73619**	Rheumatoid arthritis of subtalar joint
24217	Localised; primary osteoarthritis of the upper arm	**93715**	[X]Other seropositive rheumatoid arthritis
24717	Medial meniscus derangement NOS	**96712**	[X]Oth spcfc arthropathiesNEC
24747	Inflammatory polyarthropathy NOS	**97073**	Oligoarticular osteoarthritis; unspecified; of upper arm
24941	Medial menisc.derang.unspecif	**97360**	[X]Disorder of patella, unspec

Appendix III: A List of Indicative Prodcode for Pregabalin and Gabapentin

Drug	Prodcode	Drug	Prodcode
Pregabalin	790, 819, 6584, 6631, 6936, 6949, 6999, 7005, 7208, 7209, 7394, 10189, 16509, 16542, 37801, 38293, 48253, 51227, 51924, 52547, 55972, 60543, 63069, 63088, 63089, 63090, 63091, 63174, 63300, 63317, 63877, 63964, 63965, 64005, 64037, 64038, 64039, 64040, 64041, 64042, 64285, 64497, 64568, 65069, 65073, 65218, 65606, 65787, 65863, 66509, 66941, 67053, 67184, 67384, 67440, 68014, 68441, 69034, 69125, 69296, 69418, 69497, 69498, 69499, 69501, 69554, 69781, 69799, 69877, 69987, 70064, 70229, 70478, 70544, 70545, 70546, 70648, 70729, 70730, 70731, 70735, 71221, 71313, 71461, 71533, 71659, 73026, 73424, 73584, 73817, 76318, 77847, 78146, 80333, 80564, 80667, 80687, 80705, 80743, 80762, 80801	**Gabapentin**	660, 1584, 4781, 5221, 6304, 7538, 10007, 16215, 17564, 18211, 25815, 27454, 28713, 34506, 34606, 34716, 34946, 44022, 44187, 44261, 47579, 48035, 48060, 51118, 53296, 53784, 54609, 55535, 55624, 57120, 57527, 57649, 58162, 58382, 58383, 58472, 58960, 59147, 59196, 60389, 61266, 63375, 63432, 64213, 64302, 64306, 64981, 66617, 67091, 67969, 68047, 68049, 69914, 70247, 70459, 70506, 70738, 70954, 71013, 72849, 73047, 73587, 73635, 76014, 76435, 76604, 77136, 77695, 78410, 78641, 78801, 79400, 80504, 81124

Appendix IV: List of indicative Medcode for cancer diagnosis

Medcode	Term	Medcode	Term
318	Malignant neoplasm of glottis	**10949**	Malignant neoplasm of ampulla of Vater
319	Malignant neoplasm of larynx	**10995**	Malignant neoplasm of other and unspecified sites
779	Malignant neoplasm of urinary bladder	**11035**	Primary malignant neoplasm of unknown site
780	Malignant neoplasm of prostate	**11178**	Warthin's tumour
865	Malignant melanoma of skin	**11628**	Cancer of bowel
1056	Malignant neoplasm of other and unspecified site NOS	**11754**	[M]Sclerosing stromal tumour
1062	Malignant neoplasm of oesophagus	**11991**	Primary vulval cancer
1220	Malignant neoplasm of colon	**12323**	Malignant neoplasm of lymphatic and haemopoietic tissue
1599	Malignant neoplasm of kidney parenchyma	**12335**	Malignant lymphoma NOS
1800	Malignant neoplasm of rectum	**12389**	Malignant neoplasm of renal pelvis
1952	Secondary malignant neoplasm of kidney	**12490**	Malignant neoplasm of nose NOS
1986	Cancer of ovary	**12499**	[X]Malignant neoplasm of breast
2492	Malignant neoplasm of skin NOS	**12582**	Malignant neoplasm of lower lobe of lung
2587	Lung cancer	**12870**	Malignant neoplasm of main bronchus
2744	Malignant neoplasm of uterus, part unspecified	**13243**	Malignant neoplasm of trachea, bronchus and lung
2747	Malignant neoplasm of cervix uteri	**13252**	Malignant neoplasm of genitourinary organ
2755	Cancers	**13558**	Suspected lung cancer
2815	Malignant neoplasm of sigmoid colon	**14712**	Malignant neoplasm of lip
2890	Malignant neoplasm of endometrium of corpus uteri	**14792**	Malignant neoplasm of other and unspecified parts of mouth
3213	Malignant neoplasm of corpus uteri, excluding isthmus	**14800**	Malignant neoplasm of stomach NOS
3541	Malignant neoplasm of penis and other male genital organs	**15027**	Malignant lymphoma NOS
3811	Malignant neoplasm of caecum	**15036**	Malignant mast cell tumours
3903	Malignant neoplasm of bronchus or lung NOS	**15103**	Secondary malignant neoplasm of liver
3968	Malignant neoplasm of female breast	**15148**	Malignant neoplasm of testis
4156	Sternomastoid tumour	**15169**	Glomus tumour
4218	Malignant neoplasm of parathyroid gland	**15182**	Malignant neoplasm of connective and soft tissue, site NOS
4388	Malignant neoplasm of parotid gland	**15221**	Malignant neoplasm of trachea

4554	Malignant neoplasm of vulva unspecified	**15223**	Malignant neoplasm of ureter
4632	Other malignant neoplasm of skin	**15377**	Malignant essential hypertension

Medcode	Term	Medcode	Term
4865	Oesophageal cancer	**15504**	Malignant lymphoma NOS of lymph nodes of multiple sites
5116	Mixed parotid tumour	**15543**	[M]Neoplasm, uncertain whether benign or malignant
5198	Secondary malignant neoplasm of brain	**15644**	Malignant neoplasm of urethra
5443	Malignant neuroleptic syndrome	**15684**	Malignant neoplasm of frontal sinus
5637	Malignant neoplasm of thyroid gland	**15709**	Malignant neoplasm of digestive organs and peritoneum
5842	Secondary malignant neoplasm of other specified sites	**15711**	Malignant neoplasm cerebrum (excluding lobes and ventricles)
5932	[M]Tumour cells, uncertain whether benign or malignant	**15868**	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
6751	[M]Granulosa cell tumour NOS	**15907**	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
6806	Malignant neoplasm of small intestine and duodenum	**15976**	Malignant neoplasm of abdomen
6895	[M]Tumour cells, benign	**15991**	Malignant neoplasm of choroid
6935	Malignant neoplasm of transverse colon	**16075**	Malignant neoplasm of bone and articular cartilage NOS
7046	Malignant neoplasm of body of uterus	**16105**	Malignant neoplasm of gallbladder
7593	Malignant pleural effusion	**16202**	Malignant neoplasm of skin of nose (external)
7654	Secondary malignant neoplasm of bone and bone marrow	**16213**	Secondary malignant neoplasm of pleura
7805	Malignant neoplasm of ovary	**16241**	Malignant neoplasm of tonsil
7982	Malignant neoplasm of common bile duct	**16280**	Malignant neoplasm of neck NOS
8154	Malignant ascites	**16297**	Malignant neoplasm of pharynx unspecified
8166	Malignant neoplasm of pancreas	**16298**	Malignant neoplasm of retroperitoneum and peritoneum NOS
8386	Malignant neoplasm of stomach	**16460**	[M]Malignant lymphoma, non Hodgkin's type
8550	Malignant neoplasm of pituitary gland	**16500**	Secondary malignant neoplasm of other specified site NOS
8627	[M]Tumour cells, malignant	**16704**	Malignant neoplasm of vertebral column
8771	Malignant neoplasm of head of pancreas	**16760**	Secondary malignant neoplasm of breast
8918	Malignant neoplasm of liver and intrahepatic bile ducts	**16915**	Malignant neoplasm of intrahepatic bile ducts
9030	Malignant neoplasm of other and ill-defined sites	**16967**	Malignant neoplasm of overlapping lesion of corpus uteri
9088	Malignant neoplasm of hepatic flexure of colon	**17314**	[M]Wilms' tumour
9237	Malignant neoplasm of larynx NOS	**17366**	[M]Soft tissue tumours and sarcomas NOS

9303	Suspected bladder cancer	**17391**	Malignant neoplasm of carina of bronchus
9470	Malignant neoplasm of female breast NOS	**17404**	Suspected prostate cancer
9505	Secondary malignant neoplasm of skin of breast	**17475**	Malignant neoplasm of maxilla
Medcode	**Term**	**Medcode**	**Term**
9618	Secondary and unspecified malignant neoplasm of lymph nodes	**17559**	Malignant neoplasm of intestinal tract, part unspecified
9622	Malignant neoplasm of cauda equina	**17841**	Malignant neoplasm of glans penis
10283	Malignant neoplasm of tongue	**17887**	Malignant lymphoma otherwise specified
10358	Malignant neoplasm of upper lobe, bronchus or lung	**17912**	Malignant neoplasm, overlapping lesion of floor of mouth
10698	Malignant neoplasm of vaginal vault	**18065**	[M]Sertoli-Leydig cell tumour
10805	[M]Epithelial tumour, benign	**18245**	Malignant neoplasm of skin of lip
10851	Cerebral tumour - malignant	**18266**	[M]Granular cell tumour NOS
10864	Malignant neoplasm of descending colon	**18314**	Malignant neoplasm of bone and articular cartilage
10923	Suspected brain tumour	**18354**	Malignant neoplasm of other specified skin sites
10946	Malignant neoplasm of ascending colon	**18613**	Malignant neoplasm of duodenum

Appendix V: List of Indicative Medcode for Epilepsy Diagnosis

Medcode	Term	Medcode	Term
573	Epilepsy	**26733**	Partial epilepsy without impairment of consciousness OS
988	Grand mal (major) epilepsy	**27526**	Partial epilepsy without impairment of consciousness NOS
1715	Epileptic absences	**30604**	Alcohol-induced epilepsy
2907	Petit mal (minor) epilepsy	**30635**	Photosensitive epilepsy
3175	Temporal lobe epilepsy	**30816**	Drug-induced epilepsy
3607	Fit (in known epileptic) NOS	**31830**	Epileptic seizures - akinetic
3783	H/O: epilepsy	**31877**	[X]Schizophrenia-like psychosis in epilepsy
4093	Status epilepticus	**31920**	Partial epilepsy with impairment of consciousness NOS
4109	Traumatic epilepsy	**32288**	Partial epilepsy with impairment of consciousness
4478	Infantile spasms	**34079**	Epileptic automatism
4602	Nocturnal epilepsy	**34473**	Epilepsy treatment started
4801	Epileptic seizures - myoclonic	**34792**	Lennox-Gastaut syndrome
5117	Grand mal status	**35217**	DNA - Did not attend epilepsy clinic
5152	Epileptic seizures - tonic	**36203**	Psychosensory epilepsy
5525	Focal epilepsy	**37592**	Somatosensory epilepsy
5668	Grand mal seizure	**37644**	Progressive myoclonic epilepsy
6271	Status epilepticus, unspecified	**37782**	Neonatal myoclonic epilepsy
6709	[X]Epileptic psychosis NOS	**38307**	Other forms of epilepsy
6983	Epilepsy monitoring	**38919**	Transient epileptic amnesia
7807	Last fit	**39023**	West syndrome
7809	O/E - petit mal fit	**39160**	Many seizures a day
7945	Hypsarrhythmia	**40105**	Simple partial epileptic seizure
8097	Absence seizure	**40806**	Generalised convulsive epilepsy NOS
8187	Tonic-clonic epilepsy	**40863**	Epilepsy impairs education
8262	Fit frequency	**43679**	[X]Acquired aphasia with epilepsy [Landau - Kleffner]
8385	Epilepsy resolved	**44252**	Generalised nonconvulsive epilepsy NOS
9569	Jacksonian, focal or motor epilepsy	**45602**	Myoclonic encephalopathy
9747	Epilepsy NOS	**45927**	Other specified generalised convulsive epilepsy
9886	Petit mal status	**46603**	Emergency epilepsy treatment since last appointment
9887	Locl-rlt(foc)(part)idiop epilepandepilptic syn seiz locl onset	**47117**	Seen in epilepsy clinic
9979	Other forms of epilepsy NOS	**48134**	Sensory induced epilepsy
11015	Seizure free >12 months	**48462**	[X]Limbic epilepsy personality
11186	Generalised nonconvulsive epilepsy	**49322**	Infantile spasms NOS
11394	Complex partial epileptic seizure	**49340**	Otohara syndrome

11752	Patient on maximal tolerated anticonvulsant therapy	**49889**	Acquired epileptic aphasia
12848	Epilepsy resolved	**50012**	Epilepsy associated problems
13219	No seizures on treatment	**50702**	Epilepsy prevents employment
Medcode	**Term**	**Medcode**	**Term**
13220	Epilepsy control poor	**51517**	O/E - psychomotor fit
13221	2 to 4 seizures a month	**51998**	Ohtahara syndrome
17399	Juvenile absence epilepsy	**52632**	No epilepsy drug side effects
18471	Epileptic seizures - clonic	**53483**	Gelastic epilepsy
18899	Daily seizures	**54165**	Epilepsy medication review
19170	Benign Rolandic epilepsy	**55260**	Cursive (running) epilepsy
19363	Juvenile myoclonic epilepsy	**55665**	Limbic system epilepsy
19549	1 to 7 seizures a week	**55706**	Epilepsy management plan given
19550	Epilepsy control good	**55739**	Visual reflex epilepsy
19551	Epilepsy care arrangement	**56359**	Menstrual epilepsy
19552	Epilepsy does not limit activities	**57277**	O/E - focal (Jacksonian) fit
20566	Epilepsy treatment stopped	**59120**	[X]Other status epilepticus
21885	Post-ictal state	**59185**	Other specified generalised nonconvulsive epilepsy
22341	Epilepsy confirmed	**59806**	Landau-Kleffner syndrome
22804	Tonic-clonic epilepsy	**65673**	Stress-induced epilepsy
22991	Epilepsy severity	**65699**	Motor epilepsy
23415	Salaam attacks	**68486**	Lightning spasms
23634	Psychomotor epilepsy	**68946**	Unilateral epilepsy
24309	Epileptic seizures - atonic	**69831**	[X]Other epilepsy
25330	Complex partial status epilepticus	**71719**	Kojevnikov's epilepsy
26015	Partial epilepsy without impairment of consciousness	**71801**	[X]Status epilepticus; unspecified
26144	Generalised convulsive epilepsy	**73542**	Visceral reflex epilepsy
26511	Follow-up epilepsy assessment	**96641**	Panayiotopoulos syndrome
26512	Epilepsy treatment changed	**98870**	Partial epilepsy with autonomic symptoms
26618	1 to 12 seizures a year	**99548**	Pykno-epilepsy
26619	Epilepsy limits activities	**99731**	[X]Other generalized epilepsy and epileptic syndromes
26620	Epilepsy restricts employment		

Appendix VI: Sensitivity Analysis Results of Additional Time Points in the Policy Development

Key words	Description
Time_month	Is β1 estimates the change in the prevalence number of gabapentinoid users per 10,000 registrants that occurs with each month before the intervention (i.e. the baseline trend)
Intervention	Is β2 estimates the level change in the monthly prevalence number of gabapentinoid users per 10,000 registrants immediately after the intervention, that is, from the end of the preceding segment
Time after intervention	Is β3 estimates the change in the trend in the monthly prevalence number of gabapentinoid users per 10,000 registrants after the application of the intervention, compared with the monthly trend before the intervention

A. First pregabalin abuse case (January 2013)

Dependent variable	coefficients	Std. Err.	t	Sig
Monthly prevalence of gabapentin users[1]				
β0 (constant)	17.35521	2.959298	5.86	0.000
β1	-1.974323	0.144768	-13.64	0.000
β2	1.282989	0.4621364	2.78	0.007
β3	1.945324	0.1568194	12.40	0.000
Monthly prevalence of pregabalin users[2]				
β0 (constant)	14.04502	4.24969	3.30	0.001
β1	-1.158008	0.850285	-1.36	0.177
β2	0.5111799	1.121685	0.46	0.650
β3	1.153885	0.8503647	1.36	0.178

Std. Err.: Standard error; t: t-value; sig: probability
3 This is the result of Regression after correction of autocorrelation with Newey-West standard errors regression
4 This is the result of Regression after correction of autocorrelation

Interpretation:

There was no significant difference in the baseline trend of monthly pregabalin users before the first pregabalin abuse case, in the level immediately after the first case and in the trend after the first pregabalin abuse case competed to the baseline trend**.**

There was a significant decrease in the baseline trend of the monthly gabapentin users before the first case of pregabalin abuse. However, there was a significant increase in the number of gabapentin users immediately and after the first pregabalin abuse case compared to the baseline trend.

B. Publication of advice about the risk of Gabapentinoid misuse (December 2014)

Dependent variable	coefficients	Std. Err.	t	Sig
Monthly prevalence of gabapentin users[1]				
β0 (constant)	16.75512	4.798774	3.49	0.001
β1	0.096093	0.1664614	0.58	0.565
β2	0.8575625	1.006183	0.85	0.396
β3	-0.1700488	0.1719411	-0.99	0.325
Monthly prevalence of pregabalin users[2]				
β0 (constant)	14.63744	3.405738	4.30	0.000
β1	0.0850055	0.0350859	2.42	0.017
β2	-0.4159865	0.5273194	-0.79	0.432
β3	-0.1050477	0.038027	-2.76	0.007

Std. Err.: Standard error; t: t-value; sig: probability
1 This is the result of Regression after correction of autocorrelation with Newey-West standard errors regression
2 This is the result of Regression after correction of autocorrelation

Interpretation:

No significant change was noticed in the monthly prevalence of pregabalin users in the baseline trend and the level immediately after the publication. However, there was a statistical significant decrease in the monthly trend after the publication of advice about the risk of gabapentinoid misuse.

No significant change was noticed in the monthly prevalence of gabapentin users in the baseline trend, the level and the monthly trend after the publication of advice about the risk of gabapentinoid misuse.

C. Publication of Advisory Council on the Misuse of Drugs about recommendation of Gabapentinoid classification (January 2016)

Dependent variable	coefficients	Std. Err.	t	Sig
Monthly prevalence of gabapentin users[1]				
β0 (constant)	29.86465	5.714152	5.23	0.000
β1	0.0735226	0.0407404	1.80	0.075
β2	-1.9267	0.744025	-2.59	0.011
β3	-0.211784	0.0563398	-3.76	0.000
Monthly prevalence of pregabalin users[2]				
β0 (constant)	18.26188	3.668446	4.98	0.002
β1	0.0723277	0.0222589	3.25	0.002
β2	-1.891789	0.5851208	-3.23	0.002
β3	-0.0785254	0.0249827	-3.14	0.000

Std. Err.: Standard error; t: t-value; sig: probability
1 This is the result of Regression after correction of autocorrelation with Newey-West standard errors regression
2 This is the result of Regression after correction of autocorrelation

Interpretation:

There was a significant decrease in the number of gabapentin and pregabalin users after the publication of the ACMD recommendations to reclassify gabapentinoid to be controlled drug as class C substances. The decrease was in the level and the monthly trend compared to the baseline trend.

Appendix VII: ICD-10 and Read Codes for Overdose Diagnosis

A. Read and Med codes for overdose diagnosis within CPRD

READ code	Med code	Term
SL...15	**171**	Overdose of drug
U20..11	**697**	[X]Deliberate drug overdose / other poisoning
SLHz.00	**713**	Drug and medicament poisoning NOS
T8...11	**1493**	Cause of overdose - accidental
TK05.00	**2557**	Suicide + selfinflicted poisoning by drug or medicine NOS
U1A..12	**3390**	[X]Accidental drug overdose / other poisoning
TK...11	**6595**	Cause of overdose - deliberate
14K0.00	**13568**	H/O: repeated overdose
T8z..00	**17941**	Accidental poisoning by drugs NOS
SL...00	**19968**	Poisoning
SL...12	**20409**	Drug poisoning
U1A..11	**20879**	[X]Accidental drug / other poisoning
TK04.00	**22199**	Suicide + selfinflicted poisoning by other drugs/medicines
T88yz00	**33639**	Accidental poisoning by other drugs NOS
T85..00	**34039**	Accidental poisoning by other drugs acting on nervous system
U208.00	**35879**	[X]Int self poison/exposure to other/unspec drug/medicament
SLHy.00	**35929**	Other drug and medicament poisoning OS
T88y.00	**38037**	Accidental poisoning by other drugs OS
SL6xz00	**41097**	Anticonvulsant poisoning NOS
U1A0000	**42555**	[X]Accident poison/exposure to nonopioid analgesic at home
SL...13	**47691**	Medicinal poisoning
U201000	**53204**	[X]Int self poison/exposure to antiepileptic at home
SLX..00	**57661**	Poisoning by oth and unspec antipsychotics and neuroleptics
SL6..11	**62030**	Anticonvulsant poisoning
U201.00	**65955**	[X]Intent self poison/exposure to antiepileptic
U201z00	**66117**	[X]Intent self poison antiepileptic unspecif place
TN05.00	**67988**	Injury ?accidental, poisoning by drug or medicament NOS
T850.11	**68758**	Accidental poisoning by anticonvulsant
U1A1.00	**69744**	[X]Accident poisoning/exposure to antiepileptic
14K1.00	**99775**	Intentional overdose of prescription only medication
SL6x.00	**99845**	Other anticonvulsant poisoning
U1A1000	**101273**	[X]Accident poison/exposure to antiepileptic at home
1JP..00	**103643**	Suspected drug overdose
SyuFG00	**113985**	[X]Poisoning by mixed antiepileptics, NEC

B. ICD_10 codes for overdose to use in HES

ICD 10 Code	Term
X40-X49	Accidental poisoning by and exposure to noxious substance including antiepileptic drugs
X60-69	Intentional self-poisoning by and exposure to noxious substance including antiepileptic drugs
X85	Poisoning by drugs, medicaments and biological substances
X90	Poisoning, other or unspecified exposure
T36-T50	Poisoning by illicit drugs, medications, and biological substances including antiepileptic drugs
Y10	Poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent
Y11	Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent
Y13	Poisoning by and exposure to other drugs acting on the autonomic nervous system, undetermined intent
Y14	Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent
F11	Mental and behavioural disorders due to use of opioids
F12	Mental and behavioural disorders due to use of cannabinoids
F13	Mental and behavioural disorders due to use of sedatives or hypnotics
F14	Mental and behavioural disorders due to use of cocaine
F15	Mental and behavioural disorders due to use of other stimulants, including caffeine
F16	Mental and behavioural disorders due to use of hallucinogens
F19	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances

Appendix VIII: History of Substance Use Disorder Codes

Medcode	Term	Medcode	Term
689	Heroin dependence	**52815**	[X]Mental and behav dis due to vol solvents: dependence synd
1588	Misuse of drugs NOS	**52841**	Nondependent amphetamine/psychostimulant abuse, continuous
2081	Alcoholism	**52842**	Nondependent mixed drug abuse in remission
2082	Alcohol withdrawal syndrome	**52846**	Nondependent other drug abuse in remission
2083	Alcohol detoxification	**52953**	Nondependent mixed drug abuse, episodic
2084	Alcohol dependence syndrome	**53008**	Nondependent mixed drug abuse
2925	Alcoholic polyneuropathy	**53071**	Nondependent cannabis abuse in remission
3216	Acute alcoholic hepatitis	**53678**	Combined drug dependence, excluding opioid, continuous
3519	Drug addiction	**54356**	Drug abuse monitoring
3635	Nondependent cannabis abuse	**54505**	Other alcoholic dementia
4500	Korsakov's alcoholic psychosis	**54800**	Nondependent other drug abuse, continuous
4564	[X]Heroin addiction	**54983**	[X]Mental and behav dis due to hallucinogens: psychotic disord
4743	Alcoholic cirrhosis of liver	**56179**	[X]Mental and behav dis due hallucinogens: withdrawal state
4915	Alcoholic cardiomyopathy	**56194**	Combined opioid with other drug dependence, unspecified
5105	Drug dependence	**56337**	Nondependent mixed drug abuse, unspecified
5203	Glue sniffing dependence	**56410**	Delivery of rehabilitation for alcohol addiction
5610	Nondependent hallucinogen abuse	**56504**	[X]Mental and behav dis due to cannabinoids: dependence synd
5611	[X]Mental and behavioural disorders due to use of alcohol	**56650**	[X]Ment/beh dis oth stims inc caffeine: unsp ment/behav disd
5740	Acute alcoholic intoxication in alcoholism	**56947**	Continuous acute alcoholic intoxication in alcoholism
5758	[X]Chronic alcoholism	**56948**	[X]Men/beh dis mlt drg use/oth subs: resid/late psychot dis
6111	Drug addictn therap-methadone	**57574**	[X]Mnt/bh dis due cannabinds: resid and late-onset psychot dis
6169	Alcohol dependence syndrome NOS	**57714**	Alcohol dependence with acute alcoholic intoxication
6467	[X]Alcoholic hallucinosis	**57939**	Pathological alcohol intoxication
7123	[V]Personal history of alcoholism	**58145**	Follow up substance misuse assessment

7496	Drug addiction therapy	**58560**	Severity of opiate dependence questionnaire
7602	Chronic alcoholic hepatitis	**58731**	Nondependent opioid abuse, continuous
7747	Nondependent abuse of drugs	**58743**	Drug addiction notif NOS
Medcode	**Term**	**Medcode**	**Term**
7885	Alcoholic liver damage unspecified	**58934**	Nondependent cocaine abuse in remission
7943	Alcoholic hepatitis	**59009**	[X]Mental and behav dis due volatile solvents: harmful use
8284	Cannabis type drug dependence	**59163**	[X]Mnt/bh dis oth stm inc caffne resid/late-onset psycht dis
8363	Oesophageal varices in alcoholic cirrhosis of the liver	**59184**	Glue sniffing dependence NOS
8430	H/O: alcoholism	**59533**	Intramuscular drug user
8490	Drug user	**59574**	Acute alcoholic intoxication in remission, in alcoholism
8608	Analgesic abuse	**60180**	Nondependent hypnotic or anxiolytic abuse
9273	Substance abuse counselling	**60243**	SODQ - Severity of opiate dependence questionnaire
9489	Under care of community alcohol team	**60355**	Methadone maintenance
9615	[X]Drug addiction NOS	**60372**	Drug addict re-notif to CMO
10045	[X]Drug addiction-other stimul	**60420**	[X]Ment behav dis due use crack cocaine: acute intoxication
10538	[X]Drug addiction - opioids	**60676**	[X]Mental/behav dis multi drg use/psychoac subs: acute intox
10655	[X]Mental and behavioural disorders due to use cannabinoids	**61342**	[X]Mental and behav dis due seds/hypntcs: withdrawal state
10656	[X]Men and behav disorder multiple drug use/psychoactive subst	**62000**	[X]Men and behav dis due alcoh: resid and late-onset psychot dis
10691	Alcoholic fatty liver	**62106**	[X]Men and beh dis vol solvents: withdrawal state wth delirium
10860	Nondependent cocaine abuse	**62490**	Drug misuse - enhanced service completed
11106	Korsakov's alcoholic psychosis with peripheral neuritis	**62717**	Combined drug dependence, excluding opioid, episodic
11670	[X]Korsakov's psychosis, alcohol induced	**62887**	Nondependent mixed drug abuse, continuous
11746	[X]Drug addiction - cocaine	**62959**	[X]Mental and behav dis mlti drg/oth psychoa sbs: harmfl use
11840	Cocaine type drug dependence	**63076**	Nondependent other drug abuse, unspecified
12353	[X]Mental and behav dis due to use alcohol: psychotic disorder	**63379**	Drug dependence during pregnancy - baby delivered
12651	H/O: drug abuse	**64101**	[X]Men and behav dis due alcohl: withdrawl state with delirium
12856	Referral to drug abuse counsellor	**64210**	[X]Mental and behav dis due seds/hypntcs: acute intoxication
12977	Very heavy drinker - >9u/day	**64265**	Combined opioid with other drug dependence, continuous

12984	Very heavy drinker	**64269**	Other specified drug dependence in remission
14809	Combined drug dependence, excluding opioids	**64277**	Combined opioid with other drug dependence, episodic
Medcode	**Term**	**Medcode**	**Term**
16161	Nondependent other drug abuse	**64308**	[X]Men/behav dis due to use cannabinoids: oth men/behav disd
16225	Alcohol withdrawal delirium	**64316**	Nondependent other drug abuse NOS
16237	Alcoholic psychoses	**64338**	Nondependent cocaine abuse NOS
16243	Opioid type drug dependence	**64382**	Nondependent opioid abuse, episodic
16374	Methadone dependence	**64389**	[X]Ment and behav dis due use alcohol: unsp ment and behav dis
17259	[X]Delirium tremens, alcohol induced	**64500**	Pregnancy and drug dependence
17330	Alcoholic hepatic failure	**64983**	Nondependent other drug abuse, episodic
17607	[X]Alcoholic psychosis NOS	**64987**	[X]Ment/behav dis due use cannabinoids: unsp ment/behav disd
18285	Tranquilliser abuse	**65681**	[X]Mental and behav dis due cannabinoids: withdrawal state
18636	Wernicke-Korsakov syndrome	**65754**	Alcohol-induced pseudo-Cushing's syndrome
19554	FH: Alcoholism	**65826**	[X]Mental and behav dis due to hallucinogens: dependence syn
19921	Other adjustment reaction with withdrawal	**65927**	Drug addict-notify local SMR22
20514	[X]Mental and behav dis due to use alcohol: withdrawal state	**65932**	[X]Alcoholic jealousy
20962	Episodic opioid dependence	**65942**	Nondependent hypnotic or anxiolytic abuse, episodic
21087	Ecstasy type drug dependence	**65950**	[X]Mnt/bh dis mlti drg use/oth psy sbs: wthdr state + dlrium
21096	[V]Personal history of psychoactive substance abuse	**66187**	[X]Mental and behav dis due hallucinogens: acute intoxicatn
21623	Drug addict notific admin	**66243**	Nondependent hypnotic or anxiolytic abuse, unspecified
21624	Episodic acute alcoholic intoxication in alcoholism	**66404**	Maudsley addiction profile
21650	Admitted to alcohol detoxification centre	**67098**	Drug dependence during pregnancy - baby not yet delivered
21662	[X]Drug addiction - cannabis	**67462**	Nondependent hallucinogen abuse in remission
21683	LSD dependence	**67491**	[X]Mental and behav dis due to use hallucinogens: harmfl use
21713	Alcoholic fibrosis and sclerosis of liver	**67535**	[X]Mental and behav dis due to use cocaine: withdrawal state
21879	[X]Mental and behav dis due to use of alcohol: harmful use	**67651**	Alcoholic psychosis NOS
22059	Morphine dependence	**68111**	Other alcoholic psychosis NOS
22079	Injecting drug user	**68150**	Hallucinogen dependence NOS
22186	Amphetamine or other psychostimulant dependence	**68396**	Nondependent hypnotic or anxiolytic abuse in remission
22481	Nondependent amphetamine or other psychostimulant abuse	**68658**	Tobacco dependence NOS

22730	Steroid abuse	**69138**	[X]Mental and behav dis due to seds/hypntcs: psychotic disordr
23712	Hemp dependence	**69508**	Nondependent opioid abuse NOS
Medcode	**Term**	**Medcode**	**Term**
24064	Continuous chronic alcoholism	**69542**	Substance use disorder diagnostic schedule
24379	[X]Abuse of steroids or hormones	**69963**	Drug addict re-notific due
24441	Opioid drug dependence NOS	**70578**	Hallucinogen dependence in remission
24485	Chronic alcoholism in remission	**70746**	Tobacco dependence, continuous
24616	Cannabis dependence, unspecified	**70761**	Glue sniffing dependence in remission
24637	[X]Ment/behav dis mlti drug use/oth psyc sbs: psychotc dis	**70900**	Combined drug dependence, excluding opioid, in remission
24849	Drug addict notific to CMO	**70961**	[X]Ment/beh dis multi drug use/oth psy sbs unsp mnt/beh dis
24984	Alcohol-induced chronic pancreatitis	**71060**	Nondependent hallucinogen abuse, unspecified
24998	Other specified drug dependence, continuous	**71086**	Hallucinogen dependence, continuous
25110	Alcohol withdrawal hallucinosis	**71761**	CAAP - Cocaine abuse assessment profile
25175	Misuse of prescription only drugs	**72342**	Combined drug dependence, excluding opioid, NOS
25229	Nondependent amphetamine or psychostimulant abuse, episodic	**72371**	Lysergic acid diethylamide dependence
25352	Cocaine abuse assessment profile	**72564**	Other specified drug dependence, episodic
25448	Nondependent cannabis abuse, episodic	**72663**	Substance misuse clinical management plan reviewed
25526	Nondependent cannabis abuse NOS	**72700**	[V]Personal history of tobacco abuse
25527	[X]Cold turkey, opiate withdrawal	**72706**	Tobacco dependence in remission
25646	Amphetamine or psychostimulant dependence NOS	**72712**	[X]Ment/behav dis due to use oth stims inc caff: harmful use
25670	Stimulant dependence	**73448**	Hallucinogen dependence, episodic
25748	Cocaine dependence, continuous	**73737**	Combined opioid with other drug dependence NOS
25757	[X]Drug addiction- sedative / hypnotics	**73876**	[X]Alcohol deterrents caus adverse effects in therapeut use
25808	Cocaine dependence, unspecified	**78442**	H/O cannabis misuse
25925	Prolonged high dose use of cannabis	**81441**	H/O ecstasy misuse
26061	Combined opioid with other drug dependence	**82471**	H/O cocaine misuse
26096	Smokes drugs	**82476**	Previous history of cannabis misuse
26106	Episodic chronic alcoholism	**82479**	H/O heroin misuse
26323	[X]Alcoholic dementia NOS	**83564**	H/O infrequent cannabis misuse
26831	Nondependent opioid abuse	**83574**	Previous history of amphetamine misuse

27342	Alcoholic dementia NOS	**84156**	Previous history of cocaine misuse
27652	[X]Men and beh dis due opioids: resid and late-onset psychot dis	**84215**	H/O solvent misuse
Medcode	**Term**	**Medcode**	**Term**
27960	Opioid dependence in remission	**85091**	H/O daily cocaine misuse
28642	Substance misuse increased	**85096**	H/O amphetamine misuse
28766	Persistent substance misuse	**85097**	H/O methadone misuse
28780	[X]Alcohol addiction	**85671**	Previous history of crack cocaine misuse
28976	Drug addiction detoxification therapy - methadone	**85834**	H/O benzodiazepine misuse
29075	Barbiturate abuse	**85953**	Does not use heroin on top of substitution therapy
29446	Drug dependence NOS	**85956**	History of substance misuse
29691	Aversion therapy - alcoholism	**86002**	H/O daily heroin misuse
29728	Drug addiction notification	**86034**	[X]Mental behav disorders due use crack cocaine: harmful use
30094	Advice on drugs of addiction	**86035**	H/O crack cocaine misuse
30162	[X]Alcoholic paranoia	**86036**	H/O opiate misuse
30251	Intravenous drug user	**86041**	Uses heroin on top of substitution therapy
30404	Alcoholic paranoia	**86754**	H/O daily cannabis misuse
30465	DNA - Did not attend substance misuse clinic	**86771**	Previous history of methadone misuse
30481	[X]Abuse of non-dependence-producing substances	**87002**	H/O infrequent cocaine misuse
30565	Failed heroin detoxification	**87502**	H/O weekly cannabis misuse
30598	Opiate dependence detoxification	**88372**	Previous history of heroin misuse
30604	Alcohol-induced epilepsy	**88760**	H/O daily opiate misuse
30679	Drug dependence home detoxification	**88781**	H/O infrequent amphetamine misuse
30694	Drug addiction maintenance therapy - methadone	**88782**	H/O weekly amphetamine misuse
30695	Harmful alcohol use	**88844**	H/O infrequent crack cocaine misuse
30711	[V]Personal history of drug abuse by injection	**88990**	H/O daily crack cocaine misuse
30750	Delivery of rehabilitation for drug addiction	**89145**	H/O infrequent heroin misuse
31213	Substance misuse monitoring	**89698**	Previous history of ecstasy misuse
31443	Chronic alcoholism	**89930**	Previous history of solvent misuse
31569	Nondependent alcohol abuse in remission	**90109**	H/O weekly cocaine misuse
31736	[X]Mental and behav disorders due to use of volatile solvents	**90271**	H/O weekly crack cocaine misuse
31742	Alcoholic myopathy	**90442**	H/O infrequent ecstasy misuse
31862	Librium dependence	**90664**	H/O daily amphetamine misuse
32052	[X]Mental and behavioural disorders due to use of cocaine	**91029**	H/O infrequent opiate misuse
32640	[X]Mental and behavioural disorders due use of crack cocaine	**91256**	Previous history of opiate misuse

32653	Drug dependence self detoxification	**91260**	Combined drug dependence, excluding opioid, unspecified
32687	Tobacco dependence	**91277**	Substance misuse treatment programme completed
Medcode	**Term**	**Medcode**	**Term**
32709	Previously injecting drug user	**91577**	[X]Ment behav dis due crack cocaine: unsp ment and behav dis
32751	Psychostimulant abuse	**91801**	[X]Ment and behav dis due use opioids: unsp ment and behav dis
32804	Opium dependence	**91848**	Previous history of benzodiazepine misuse
32887	Hallucinogen dependence	**91939**	Substance misuse treatment withdrawn
32927	[X]Alcohol withdrawal-induced seizure	**92232**	H/O daily benzodiazepine misuse
32931	Nondependent cocaine abuse, unspecified	**92291**	[X]Ment/behav dis due use hallucinogens: unsp ment/behav dis
32964	Alcohol abuse monitoring	**92353**	Hallucinogen dependence, unspecified
33462	Cannabis drug dependence NOS	**92359**	H/O weekly ecstasy misuse
33493	[X]Mental and behav dis oth stim inc caffein: dependnce synd	**92404**	H/O daily methadone misuse
33585	[X]Drug addiction - solvent	**92993**	H/O infrequent benzodiazepine misuse
33635	Chronic alcoholism NOS	**93009**	[X]Men/beh dis mlt drg use/oth psy sbs: oth men and behav dis
33670	Other alcoholic psychosis	**93109**	H/O weekly methadone misuse
33774	Glue sniffing dependence, episodic	**93193**	Previous history of hallucinogen misuse
33838	Nondependent mixed drug abuse NOS	**93263**	H/O barbiturate misuse
33839	Cerebellar ataxia due to alcoholism	**93407**	[X]Mental and behav dis due to use seds/hypntcs: harmful use
33942	Cocaine drug dependence NOS	**93412**	Substance misuse
34249	[X]Mental and behav dis due to use opioids: dependence syndr	**93528**	H/O daily major tranquilliser misuse
34398	Drug misuse - enhanced services administration	**93554**	H/O weekly heroin misuse
35055	[V]Tobacco abuse counselling	**93774**	H/O weekly benzodiazepine misuse
35196	[X]Post hallucinogen perception disorder	**93850**	Referral to substance misuse service
35286	Substance misuse decreased	**93979**	Opioid antagonist therapy
35404	Reduced drugs misuse	**93980**	Opioid agonist substitution therapy
36241	[X]Mental and behav dis due to use opioids: withdrawal state	**94394**	Nondependent hypnotic or anxiolytic abuse NOS
36296	Acute alcoholic intoxication in alcoholism NOS	**94436**	Nondependent antidepressant type drug abuse NOS
36687	Alcohol deterrent poisoning	**94553**	Referral to specialist alcohol treatment service
36748	Alcoholic encephalopathy	**94686**	Self referral to substance misuse service
37316	Marihuana dependence	**95181**	Alcohol reduction programme

37389	[X]Mental and behav dis due cannabinoids: acute intoxication	**95380**	H/O daily ecstasy misuse
37472	Amphetamine or psychostimulant dependence, unspecified	**95396**	H/O daily solvent misuse

Medcode	Term	Medcode	Term
37691	[X]Chronic alcoholic brain syndrome	**95460**	Heroin maintenance
37900	DAST - Drug abuse screening test	**95610**	Tobacco dependence, unspecified
37946	Chronic alcoholic brain syndrome	**95953**	Nondependent opioid abuse in remission
38029	Misuses drugs orally	**95954**	Nondependent hypnotic or anxiolytic abuse, continuous
38034	Unspecified opioid dependence	**95955**	Nondependent hallucinogen abuse, continuous
38061	Alcohol induced hallucinations	**95956**	Nondependent hallucinogen abuse, episodic
38072	Glue sniffing dependence, unspecified	**96004**	Drug dependence during pregnancy/childbirth/puerperium NOS
38125	Subcutaneous drug user	**96009**	Substance misuse treatment declined
38360	Amphetamine or psychostimulant dependence, continuous	**96049**	Substance misuse structured counselling
38429	[X]Mental and behav dis due to cannabinoids: psychotic disordr	**96054**	Extended intervention for excessive alcohol consumptn complt
39051	Sedative abuse	**96198**	H/O hallucinogen misuse
39058	Nondependent amphetamine/psychostimulant abuse, unspecified	**96925**	Heroin misuse
39327	[X]Mental and behav dis due to use alcohol: dependence syndr	**97025**	Drug misuse behaviour
39799	[X]Mental and behav dis due to use alcohol: amnesic syndrome	**97028**	Illicit drug use
39836	Cocaine dependence, episodic	**97031**	Ecstasy misuse
39983	Nondependent cannabis abuse, continuous	**97071**	Possession of drugs
40530	Acute alcoholic intoxication, unspecified, in alcoholism	**97245**	Drug-related offending behaviour
40536	Nondependent opioid abuse, unspecified	**97261**	Brief intervention for excessive alcohol consumptn declined
40602	ADS - Alcohol dependence scale	**97309**	Advised to contact primary care alcohol worker
40720	Hashish dependence	**97375**	Glue sniffing dependence, continuous
41039	Preoccupied with substance misuse	**97488**	[X]Men and behav dis due opioid: withdrawl state with delirium
41317	[X]Mental and behavioural dis due use sedatives/hypnotics	**97561**	[X]Mental and behav dis due to use cannabinoids: amnesic syn

41473	Drug dependence in pregnancy, childbirth and the puerperium	**97578**	Misuses drugs
41476	Psychostimulant dependence	**97586**	Shared care drug misuse treatment - enhanced services admin
41920	Alcohol amnestic syndrome NOS	**97648**	Occasional drug user

Medcode	**Term**	**Medcode**	**Term**
41983	Alcohol detoxification	**97676**	Drug misuse treatment primary care - enhanced services admin
42140	Nondependent cannabis abuse, unspecified	**97680**	Declined referral to specialist alcohol treatment service
42257	Intranasal drug user	**97698**	Poly-drug misuser
42921	Drug withdrawal regime	**97811**	Sharing of drug injecting equipment
42923	Cannabis dependence, continuous	**98221**	Seen in substance misuse clinic
43075	Continuous opioid dependence	**98362**	Drug misuse assessment declined - enhanced services administ
43101	[X]Mental and behav disorder due other stimulants inc caffein	**98528**	Long-term drug misuser
43176	Nondependent amphetamine/psychostimulant abuse in remission	**98566**	Pharmacy attended for drug misuse - enhanced services admin
43193	Unspecified chronic alcoholism	**98618**	[X]Mental and behav dis due to vol solvents: psychotic disordr
43296	Hypnotic or anxiolytic abuse	**98763**	SMR25a drug misuse initial assessment form
43487	Drug addiction maintenance therapy - buprenorphine	**98914**	Drug addict
43901	Nondependent cocaine abuse, episodic	**99429**	H/O weekly solvent misuse
44131	[X]Men and beh dis due seds/hypns: withdrwl state wth delirium	**99798**	H/O anti-depressant misuse
44330	[X]Mental and behav dis due to seds/hypntcs: dependence synd	**100178**	Admission to substance misuse detoxification centre
44742	[X]Mnt/beh dis due oth stim inc caffein: acute intoxication	**100477**	Misused drugs in past
44966	Episodic use of drugs	**100632**	Methadone therapy
44991	Cannabis dependence in remission	**100723**	Substitute prescribing
45169	[X]Men and behav dis due to use alcohol: oth men and behav dis	**100935**	Health problem secondary to drug misuse
45208	[X]Mental and behav dis mlti/oth psych sbs: dependence syndr	**101377**	H/O weekly opiate misuse
45550	Substance misuse clinical management plan agreed	**101519**	[X]Mental and behav dis due to use tobacco: withdrawal state
46677	Alcohol withdrawal regime	**101571**	SUDDS - Substance use disorder diagnostic schedule
46732	Stimulant abuse	**101697**	Notified addict

46800	Amphetamine or psychostimulant dependence in remission	**101724**	H/O major tranquilliser misuse
46896	Nondependent cocaine abuse, continuous	**101738**	[X]Mental behav disord due crack cocaine: withdrawal state
46962	Nondependent antidepressant type drug abuse	**101892**	Age at starting drug misuse
47271	MAP - Maudsley addiction profile	**102247**	Extended interven for excessive alcohol consumption declined
Medcode	**Term**	**Medcode**	**Term**
47555	Cerebral degeneration due to alcoholism	**102440**	Amfetamine or psychostimulant dependence NOS
47739	[X]Mental and behav dis due to use of cocaine: harmful use	**102475**	[X]Mental behav disord due crack cocaine: psychotic disorder
47784	[X]Drug addiction - hallucinogen	**102534**	Dexamphetamine maintenance
47804	Continuous use of drugs	**102582**	[X]Mental behav disorders due use crack cocaine: depend synd
47836	Nondependent amphetamine or psychostimulant abuse NOS	**102591**	[X]Men and beh dis due cocaine: resid and late-onset psychot dis
48131	Nondependent hallucinogen abuse NOS	**103241**	Shared care drug misuse treatment
48241	[X] Adverse reaction to alcohol deterrents	**103726**	Shares drug equipment
48514	Denatured alcohol causing toxic effect	**103844**	Sniffs drugs
48760	[X]Mnt/behav dis other stimlnts inc caffeine: withdrwl state	**103881**	H/O daily anti-depressant misuse
49068	[X]Ment/behav dis due use vol solvents: unsp ment/behav dis	**103991**	[X]Mental and behav dis due to use opioids: amnesic syndrome
49565	[X]Mental and behav dis due to use cocaine: psychotic disorder	**105104**	Chases the dragon
49566	[X]Mental and behav dis due to use cocaine: acute intoxication	**105346**	[X]Mnt/bh dis due hallucngns: resid and late-onset psychot dis
49585	Amphetamine or psychostimulant dependence, episodic	**105999**	Smokes drugs in cigarette form
49618	Current drug user	**106143**	Previous history of anti-depressant misuse
49879	[X]Mental/behav dis oth stims inc caffeine: psychotic dis	**106290**	Declined consent for notification of drug misuse
50136	[X]Mental and behav dis due vol solvents: acute intoxication	**106342**	H/O infrequent methadone misuse
50265	[X]Mental and behavioural disorders due to use hallucinogens	**106365**	Benzodiazepine dependence detoxification
50302	[X]Mental and behav dis due to use cocaine: dependence syndr	**106802**	Drug misuse clinic administration
50343	[X]Mental and behav dis due to use cannabinoids: harmful use	**106958**	[X]Mental/behav dis multi drg use/oth psy sbs: amnesic syndr
50964	[X]Mental and behav dis due to use opioids: psychotic disorder	**107355**	Seen in drug misuse clinic

51052	Drug addiction detoxification therapy - buprenorphine	**107593**	Smokes drugs through a pipe
51290	[X]Mental and behav dis mlti/oth psychoa sbs: withdrwl state	**107792**	[X]Mental and behav dis due to use tobacco: dependence syndr
52451	Combined opioid with other drug dependence in remission	**109077**	Amfetamine or psychostimulant dependence, unspecified
52739	[X]Men and behav dis due to use opioids: oth men and behav dis	**109471**	H/O infrequent solvent misuse
52765	Cocaine dependence in remission	**109849**	Previous history of barbiturate misuse
52794	Cannabis dependence, episodic		

Appendix IX: Other Medications That Might Increase the Harm Prodcodes

Medication	Prodcode
Opioid	53, 86, 123, 148, 152, 158, 166, 187, 191, 213, 231, 234, 249, 320, 328, 354, 382, 396, 423, 458, 462, 495, 539, 607, 617, 620, 635, 655, 659, 701, 715, 748, 757, 826, 913, 1503, 161, 2041, 2367, 2450, 2764, 2957, 2966, 2997, 3064, 3165, 3239, 3378, 3522, 3644, 3653, 3698, 3714, 3919, 3990, 4114, 4115, 4236, 4266, 4280, 4369, 4476, 4477, 4518, 4691, 4693, 4805, 4823, 4834, 4999, 5028, 5048, 5079, 5137, 5138, 5169, 5257, 5555, 5563, 5572, 5585, 5599, 5651, 5652, 5657, 5664, 5668, 5670, 5681, 5696, 5697, 5714, 5833, 5840, 5843, 5936, 5991, 6002, 6040, 6056, 6153, 6181, 6210, 6215, 6232, 6234, 6269, 6298, 6366, 6414, 6458, 6459, 6547, 6557, 6608, 6609, 6708, 6736, 6769, 6790, 6879 ,6892, 6917, 6948, 7082, 7107, 7114, 7126, 7167, 7197, 7236, 7238, 7275, 7334, 7372, 7389, 7397, 7406, 7457, 7469, 7517, 7555, 7729, 7800, 7801, 7849, 7872, 7875, 7950, 7976, 7989, 7998, 7999, 8017, 8039, 8040, 8075, 8220, 8233, 8375, 8416, 8420, 8447, 8456, 8460, 8735, 8740, 8766, 8822, 8823, 8866, 8867, 8876, 8959, 8980, 9001, 9012, 9053, 9126, 9137, 9183, 9209, 9275, 9313, 9325, 9330, 9331, 9602, 9615, 9672, 9739, 9874, 9927, 9928, 9945, 9960, 9973,10021, 10077, 10205, 10239, 10280, 10309, 10473, 10525, 10578, 10583, 10631, 10730, 10769, 10829, 10866, 10907, 10922, 10925, 11101, 11129, 11275, 11342, 11405, 11471, 11549, 11559, 11584, 11698, 11734, 11746, 11748, 11755, 11801, 11838, 11843, 11971, 11982, 12011, 12020, 12076, 12135, 12219, 12508, 12567, 12583, 12591, 12602, 12604, 12608, 12889, 12900, 13031, 13076, 13114, 13117, 13172, 13225, 13280, 13300, 13364, 13420, 13423, 13588, 13711, 13813, 13995, 13997, 14050, 14063, 14156, 14226, 14373, 14394, 14490, 14900, 15064, 15337, 15339, 15350, 15353, 15475, 15514, 15781, 15792, 15793, 15798, 15815, 15950, 15964, 16096, 16189, 16271, 16273, 16335, 16395, 16618, 16964, 17043, 17092, 17163, 17167, 17271, 17386, 17398, 17490, 17734, 17825, 17863, 17893, 17936, 17943, 18166, 18174, 18468, 18491, 18624, 18626, 18639, 18656, 18700, 18727, 18734, 18792, 18801, 18881, 18965, 18977, 19069, 19092, 19116, 19119, 19291, 19317, 19351, 19449, 19471, 19477, 19764, 19954, 19972, 19993, 20005, 20008, 20039, 20219, 20310, 20713, 20752, 20783, 20815, 21256, 21275, 21285, 21397, 21777, 21797, 21868, 21947, 21972, 22024, 22756, 22896, 23060, 23063, 23128 23375, 23442, 23625, 23775, 23777, 23778, 23785, 23906, 23977, 23981, 24108, 24124, 24125, 24192, 24383, 24414, 24453, 24640, 24697, 24733, 24736, 24790, 24808, 24816, 24830, 24840, 24867, 24986, 25185, 25199, 25316, 25481, 25485, 25503, 25611, 25649, 25650, 25830, 25833, 25959, 25979, 26021, 26115, 26283, 26284, 26336, 26407, 26653, 26805, 26908, 26986, 27058, 27298, 27352, 27436, 27548, 27591, 27749, 28189, 28396, 28421, 28503, 28711, 28728, 28732, 28805 , 28837, 29014, 29020, 30252, 30320, 30514, 30633, 30698, 30761, 31033, 31044, 31053, 31105, 31107, 31253, 31407, 31452, 31582, 31584, 31599, 31650, 31700, 31734, 31885, 31935, 31943, 31960, 32165, 32357, 32381, 32425, 32436, 32450, 32459, 32460, 32520, 32687, 32688, 32831, 32897, 33528, 33654, 33954, 34008, 34065, 34073, 34090, 34099, 34152, 34168, 34172, 34176, 34260, 34281, 34348, 34373, 34383, 34422, 34437, 34440, 34444, 34477, 34489, 34521, 34552, 34570, 34579, 34639, 34662, 34730, 34771, 34786, 34787, 34789, 34808, 35038, 35085, 35093, 35169, 35170, 35269, 35330, 35341, 35347, 35438, 36035, 36040, 36185, 36211, 36697, 36732, 36873, 36949, 37020, 37021, 37251, 37703, 37719, 37779, 37831, 37867, 37923, 37928, 37954 37960, 37968, 38013, 38031, 38092, 38103, 38196, 38301, 38311, 38326, 38351, 38365, 38521, 38524, 38528, 38553, 38874, 38956, 38970, 38987, 39084, 39180, 39251, 39419, 39469, 39475, 39477, 39478, 39498, 39505, 39518 ,39558, 39590, 39709 ,39723, 39746, 39750, 39756, 39798, 39799, 39811, 39842, 39929,

Medication	Prodcode
Opioid	39987 ,40018, 40058 ,40060, 40061, 40098, 40128 ,40159 ,40166, 40211 ,40212, 40239 ,40249, 40254, 40427, 40434, 40473, 40508 ,40563, 40576, 40616 ,40645, 40688, 40718, 40752, 40785 ,40805, 40883, 40926, 40940, 41599, 41668, 41673, 41674, 41722, 41974, 41976, 42021, 42074, 42094, 42208, 42380, 42399, 42538, 42576, 42590, 42591, 42708, 42792, 42798, 42913, 43089, 43152, 43198, 43315, 43504, 43513 ,43550, 43617, 43652, 43657, 43720, 43812, 44311, 44371, 44487, 44837, 44867, 45092, 45325, 45439, 45460, 45549, 45598, 45736, 45745, 45766, 45788, 45790, 45800, 45811, 45827, 45830, 45894 ,45929, 45936, 45982, 46018, 46019, 46020, 46021, 46022, 46159 ,46187, 46279 ,46354, 46461 ,46555, 46559, 46560, 46587, 46643, 46657 ,46658 ,46659 ,46733, 47003 ,47072, 47154 ,47399 ,47413, 47460, 47555, 47671 ,47672 ,47753, 47759 ,47854, 47867, 47919, 47949, 47952, 47985, 48004, 48066, 48090, 48128 ,48133 ,48136, 48148, 48153 ,48158 ,48183 ,48259 ,48413 ,48434 ,48483, 48571 ,48604 ,48880, 48912 ,48913 ,48953, 48964 ,49323 ,49324, 49742, 49787 ,49791 ,49940 ,49976 ,50095 ,50380 ,50421 ,50468 ,50513 ,50532 ,50659 ,50671 ,50726, 50733 ,50862 ,50929 ,50947, 51235, 51327 ,51384 ,51611 ,51644 ,51789 ,51896 ,51937 ,52178 ,52216 ,52217 ,52220, 52400, 52495 ,52592, 52605, 52809, 52888 ,52889, 52929, 52977 ,53062 ,53106 ,53113 ,53116 ,53181 ,53273 ,53417 ,53600 ,53639 ,53709 ,53918 ,53929 ,53999 ,54017 ,54023 ,54085 ,54354 ,54406 ,54520 ,54694 ,54790, 54806 ,54979 ,55052 ,55206 ,55221 ,55304 ,55309 ,55365 ,55425 ,55724 ,55752 ,55832 ,55839 ,55852 ,56022 ,56178 ,56202 ,56329 ,56491 ,56544 ,56559 ,56581, 56665, 56670, 56671, 56788, 56817, 57027 ,57033 ,57052 ,57381, 57454, 57487 ,57623, 57750, 57752 ,58039 ,58114 ,58129 ,58131 ,58190 ,58217, 58853 ,58879, 58909 ,59057 ,59146 , 59392 ,59443 ,59473 ,59482 ,59490 ,59584 ,59618 ,59678 ,59865 ,59970 ,59978 ,59989 ,60053 ,60080 ,60082 ,60121 ,60146 ,60158 ,60170 ,60196 ,60477 ,60489 ,60507 ,60518, 60640 ,60721 ,60751 ,60759 ,60766 ,60943 ,60950 ,60958 ,61049 ,61086 ,61091 ,61100 ,61156 ,61241, 61272 ,61305 ,61400, 61423, 61506 ,61584 ,61610 ,61708 ,61744 ,61764 ,61775 ,61779 ,61836 ,61918 ,61935 ,61936 ,61942 ,62228 ,62322, 62675 ,62689 ,62776 ,62874 ,62969 ,63047 ,63139 ,63182 ,63198 ,63332 ,63340 ,63398 ,63423 ,63547, 63593, 63640 ,63714 ,63788 ,63898 ,64079 ,64108 ,64150, 64155 ,64164, 64333 ,64417 ,64426 ,64496, 64552 ,64731, 64751, 64752 ,64780, 64781, 64807 ,64847 ,64860 ,64871 ,64965 ,65118 ,65157 ,65168 ,65245, 65266 ,65269, 65359 ,65372, 65390 ,65392, 65437 ,65646 ,65689, 65932, 65933, 65954, 66115, 66121, 66280, 66298, 66299, 66336 ,66463, 66470, 66606, 66616 ,66619, 66654 ,66689, 66695, 66729, 66760, 66815, 66837, 66893
Benzodiazepin	46, 47, 664, 816, 1088, 1400, 1559, 2073, 2078, 2083, 2091, 2352, 2401, 3105, 3205, 3870, 3950, 3956, 3973, 4140, 4141, 4176, 4338, 4395, 4483, 4566, 4587, 5793, 5842, 6747, 7301, 7391, 7444, 7566, 7652, 8029, 8184, 8334, 8344, 8345, 8721, 8842, 9045, 9065, 9111, 9430, 9696, 10274,10278, 10402, 10581, 10650, 10802, 10909, 10954, 11486, 12124, 12237, 12278, 12598, 12849, 13200, 13279, 13305, 13756, 14743, 16610, 16734, 17038, 17637, 17830, 18488, 18928, 19299, 19315, 20164, 20514, 20968, 23820, 24321, 24386, 24422, 24519, 25273, 26496, 26835, 26837, 28347, 28698, 28703, 29945, 30321, 31633, 32296, 32417, 32500, 32853, 32911, 33070, 33086, 33672, 33776, 34033, 34045, 34293, 34335, 34338, 34340, 34482, 34491, 34524, 34561, 34614, 34615, 34635, 34677, 34681, 34735, 34807, 34876, 34892, 35373, 35932, 36200, 36581, 36604, 37124, 37566, 37745, 38193, 38410, 39284, 41391, 41411, 41531, 41542, 41553, 41601, 41602, 41607, 41632, 41689, 42503, 42814, 43450, 44764, 45077, 45135, 45218, 45244, 45313, 45615, 45829, 45974, 46667, 46757, 46797, 46826, 46883, 46896, 46913, 46946, 46966, 47045, 47066, 48544, 48818, 49534, 50108, 51335, 51550, 51754, 51925, 51985, 53306, 53311, 53461, 53566, 53739, 53748, 54695, 54919, 55642, 56236, 56551, 57268, 57596, 57664, 57749,, 57838, 58460, 58482, 58959, 59122, 59396, 59407, 59913, 60936, 61015, 61290, 61450, 61626, 61886, 62216, 62541, 63238, 63694,, 64200, 64505, 64693, 64729, 64876, 65238, 66878, 66879, 66889, 66891

Medication	Prodcode
Z-drugs	5306, 5352, 5916, 9598, 2017, 3126, 3741, 5459, 29869, 30981, 31710, 3384, 41539, 41696, 41697, 42089, 43560, 65190, 74636, 74652, 75866, 77396, 77581, 82315, 66, 721, 3320, 4187, 5058, 14365, 15852, 24135, 29219, 30056, 30377, 33045, 33663, 34372, 34612, 34777, 34823, 34874, 34897, 43445, 45353, 46799, 52022, 57937, 59640, 61477, 63592, 65637, 70727, 71089, 73154, 75455, 76161, 80518, 82482, 82542, 82691
Antideprressant	22, 49, 50, 67, 74, 83, 84, 114, 182, 228, 252, 301, 418, 470, 476, 487, 488, 513, 527, 595, 603, 609, 623, 648, 727, 742, 785, 815, 840, 841, 873, 1169, 1208 ,1222, 1310, 1397, 1453, 1474, 1575, 1612, 1712, 1730, 1809, 1888, 1940, 2039, 2093, 2157, 2290, 2320, 2356, 2408, 2486, 2525, 2531, 2532, 2533, 2548, 2579, 2617, 2654, 2880, 2883, 2897, 2936, 2985, 3083, 318, 3194, 3195, 3196, 3349, 3351, 3353, 3355, 3356, 3391, 3490, 3554, 3601, 3652, 3657, 3668, 3670, 3771, 3777, 3783, 3842, 3861, 3903, 3925, 3926, 3951, 3953, 3955, 4003, 4011, 4020, 4075, 4118, 4149, 4194, 4218, 4297, 4310, 4321, 4329, 4352, 4404, 4411, 4422, 4554, 4682, 4690, 4726, 4770, 4874, 4907, 5073, 5187, 5212, 5298, 5597, 5710, 5832, 6054, 6218, 6255, 6274, 6312, 6360, 6405, 6421, 6442, 6481, 6488, 6643, 6644, 6645, 6795, 6846, 6854, 6894, 6895, 7059, 7100, 7122, 7147, 7153, 7328, 7468, 7475, 7515, 7573, 7677, 7678, 7693, 7751, 7755, 7756, 7780, 7784, 7816, 7894, 7910, 7918, 7919, 7979, 7981, 8055, 8144, 8174, 8250, 8332, 8377, 8493, 8585, 8640, 8661, 8719, 8720, 8726, 8826, 8831, 8844, 8878, 8928, 9022, 9182, 9206, 9496, 9534, 10083, 10413, 10514, 10649, 10787, 10948, 11187, 11956, 11963, 12111, 12123, 12125, 12128, 12129, 12192, 12194, 12207, 12221, 12227, 12309, 12353, 12368, 12503, 12549, 12710, 13151, 13237, 13318, 13496, 13621, 14119, 14129, 14398, 14519, 14521, 14534, 14578, 14740, 14803, 14849, 14987, 15163, 15268, 15380, 15632, 16154, 16229, 16323, 16949, 16969, 17014, 17087, 17183, 17190, 17319, 17588, 18290, 18342, 18832, 18932, 19168, 19181, 19183, 19186, 19470, 19779, 20026, 20061, 20152, 20571, 20703, 20712, 20715, 21081, 21157, 21357, 21819, 21820, 22006, 22070, 22872, 23334, 23426, 23497, 24107, 24134, 24141, 24145, 24147, 24152, 24680, 24700,, 24723, 24890, 25036, 25045, 25070, 25085, 25444, 25835, 25909, 25945, 26016, 26056, 26213, 26513, 26715, 26822, 27008, 27476, 27565, 27568, 27616, 27733, 27876, 29339, 29756, 29786, 29857, 29875, 30258, 30375, 30376, 30738, 30983, 31168, 31672, 31824 31826, 32121, 32401, 32439, 32457, 32546, 32848, 32863, 32899, 33071, 33074, 33090, 33164, 33337, 33410, 33624, 33720, 33779, 33780, 33978, 34003, 34046, 34058, 34107, 34129, 34182, 34197, 34202, 34216, 34222, 34223, 34224, 34245, 34251, 34274, 34288,, 34294, 34351, 34355, 34356, 34401, 34413, 34415, 34419, 34421, 34436, 34456, 34466, 34470, 34474, 34498, 34499, 34503, 34525, 34578, 34580, 34586, 34587, 34603, 34634, 34641, 34643, 34672, 34722, 34731, 34745, 34782, 34813, 34822, 34849, 34856, 34866, 34871, 34872, 34916, 34950, 34966, 34970, 35021, 35065, 35112, 35122, 35176, 35258, 35391, 35445, 35455, 35487, 35493, 35530, 35723, 36746, 36893, 37256, 38274, 38827, 38890, 39145, 39359, 39360, 39770, 39809, 40048, 40049, 40054, 40059, 40062, 40092, 40160, 40165, 40277, 40279, 40295, 40396, 40407, 40494, 40514, 40515, 40517, 40726, 40764, 40777, 40815, 40817, 40892, 40917, 41033, 41062, 41299, 41314, 41408, 41492, 41528, 41563, 41597, 41609, 41627, 41628, 41654, 41681, 41709, 41710, 41729, 41731, 41747, 41970, 41971, 42078,42107, 42228, 42247, 42387, 42394, 42499, 42600, 42660, 42734, 42803, 43024, 43203, 43234, 43235, 43236, 43237, 43239, 43241, 43242, 43246, 43247, 43248, 43250, 43253, 43256, 43257, 43334, 43518, 51383, 51699, 51758, 52074, 52100, 52354, 52408, 52516, 52607, 52716, 52824, 52867, 53161, 53187, 54792, 54826, 54827, 54877, 54933, 55023, 55033, 55137, 55138, 55139, 55146, 55289, 55424, 55482, 55488, 60370, 60410, 60449, 60534, 60538, 60549, 60568, 60591, 60619, 60839, 60843,60888, 60895, 60929, 60962, 61236, 61335, 61503, 61547, 61657, 61835, 61842, 61856, 62155, 62335, 62620

Medication	Prodcode
Antideprressant	62681, 62688, 62692 , 62693, 62734, 62819, 62927, 62950, 63216, 63268, 63276, 63370, 63403, 70300, 70315, 70353, 70405, 70420, 70495, 70521, 70593, 70728, 70790, 70806, 70838, 70931, 70991, 71005, 71023, 71031, 71042, 71059, 71067, 71253, 71257, 71543, 71669, 71782, 71806, 71848, 71852, 71932, 72124, 72211, 72291, 72373, 72626, 72773, 73298, 73363, 73414, 73417, 73419, 73540, 73589, 73636, 73639, 73658, 73667, 73668, 73759, 73868, 73962, 74010,74011, 74190, 74516, 74557, 79590, 79628, 79766, 79768, 79784

Appendix X: Comorbidity Codes

Medcode	Term	Medcode	Term
240	Ischaemic heart disease	**24112**	[X]Single episode of psychotic depression
241	Acute myocardial infarction	**24117**	[X]Single episode of major depression and psychotic symptoms
324	Depressive disorder NEC	**24126**	Haemopericardium/current comp folow acut myocard infarct
398	Congestive heart failure	**24171**	Recurrent major depressive episodes, severe, with psychosis
462	Panic attack	**24248**	Mixed simple and mucopurulent chronic bronchitis
504	Transient cerebral ischaemia	**24351**	[X]Phobic anxiety disorder of childhood
543	[X]Depression NOS	**24446**	Cerebral infarction due to embolism of precerebral arteries
569	Infarction - cerebral	**24503**	Cardiac failure therapy
595	Endogenous depression	**24540**	Chronic coronary insufficiency
655	Anxiety with depression	**24783**	Arteriosclerotic heart disease
711	Diabetes mellitus	**25563**	Recurrent major depressive episode NOS
758	Type 2 diabetes mellitus	**25591**	Type 2 diabetes mellitus with exudative maculopathy
794	Emphysema	**25603**	Simple chronic bronchitis
884	Left ventricular failure	**25615**	Brainstem infarction
962	[X]Anxiety neurosis	**25627**	Type 2 diabetes mellitus - poor control
1001	Chronic obstructive pulmonary disease	**25697**	Recurrent major depressive episodes, severe, no psychosis
1055	Agitated depression	**25749**	Phobia counselling
1131	Neurotic depression reactive type	**25842**	Angina pectoris NOS
1195	Amaurosis fugax	**26054**	Type 2 diabetes mellitus with persistent proteinuria
1204	Heart attack	**26115**	Referral to heart failure nurse
1223	Cardiac failure	**26125**	Bronchiolitis obliterans
1268	Paroxysmal atrial fibrillation	**26306**	Chronic bullous emphysema
1298	CVA unspecified	**26424**	Infarction of basal ganglia
1344	Coronary artery disease	**26863**	New onset angina
1407	Insulin treated Type 2 diabetes mellitus	**27491**	Atypical depressive disorder
1414	Angina on effort	**27677**	Presenile dementia with depression
1430	Angina pectoris	**27685**	[X]Other phobic anxiety disorders
1431	Unstable angina	**27819**	Obstructive chronic bronchitis
1433	Transient ischaemic attack	**27884**	Decompensated cardiac failure
1446	Acute exacerbation of chronic obstructive airways disease	**27951**	Other acute and subacute ischaemic heart disease
1469	Stroke and cerebrovascular accident unspecified	**27964**	Acute heart failure
1533	Brief depressive reaction	**27975**	Cerebral infarction due to embolism of cerebral arteries
1549	Type 1 diabetes mellitus	**27977**	Other acute and subacute ischaemic heart disease NOS

Medcode	Term	Medcode	Term
1655	Triple vessel disease of the heart	**28106**	Acrophobia
1664	Atrial fibrillation	**28138**	Other chronic ischaemic heart disease
1676	Ischaemic heart disease NOS	**28167**	[X]Anxiety hysteria
1677	MI - acute myocardial infarction	**28248**	[X]Prolonged single episode of reactive depression
1678	Inferior myocardial infarction NOS	**28314**	Left sided intracerebral haemorrhage, unspecified
1723	Claustrophobia	**28554**	Angina pectoris NOS
1757	Atrial flutter	**28677**	[X]Manic-depress psychosis,depressed type+psychotic symptoms
1758	Chronic anxiety	**28736**	Acute atrial infarction
1792	IHD - Ischaemic heart disease	**28756**	[X]Seasonal depressive disorder
1895	Transient cerebral ischaemia NOS	**28863**	[X]Single episode of reactive depressive psychosis
1907	Phobic disorders	**28914**	Haemorrhagic stroke monitoring
2030	Obsessional neurosis	**28925**	Referral for guided self-help for anxiety
2062	Heart failure	**29342**	Recurrent major depressive episodes, mild
2212	Atrial fibrillation and flutter	**29421**	Silent myocardial ischaemia
2300	Phobia unspecified	**29520**	[X]Recurrent depressive disorder, current episode moderate
2417	Vertebro-basilar insufficiency	**29643**	Acute inferoposterior infarction
2491	Coronary thrombosis	**29758**	Acute transmural myocardial infarction of unspecif site
2560	Depressive psychoses	**29784**	[X]Recurrent depressive disorder, current episode mild
2571	[X]Agoraphobia	**29902**	Angina decubitus NOS
2639	Postnatal depression	**29907**	[X]Social anxiety disorder of childhood
2906	Congestive cardiac failure	**30045**	External capsule haemorrhage
2923	Puerperal depression	**30294**	Type 1 diabetes mellitus with persistent microalbuminuria
2970	[X]Depressive episode, unspecified	**30323**	Type 1 diabetes mellitus with persistent proteinuria
2972	Postviral depression	**30330**	Acute Q-wave infarct
3076	Agoraphobia with panic attacks	**30421**	Cardiac rupture following myocardial infarction (MI)
3132	Drop attack	**30779**	Heart failure annual review
3149	Cerebral infarction NOS	**31060**	Intracerebral haemorrhage in hemisphere, unspecified
3208	Obsessive-compulsive disorders	**31595**	Cortical haemorrhage
3243	Chronic bronchitis	**31757**	[X]Recurr severe episodes/psychogenic depressive psychosis
3291	[X]Depressive disorder NOS	**31957**	Social phobia, fear of public speaking
3292	[X]Recurrent depressive disorder	**32159**	Single major depressive episode, severe, with psychosis
3535	Intracerebral haemorrhage NOS	**32272**	Postoperative myocardial infarction
3704	Acute subendocardial infarction	**32450**	Ischaemic chest pain
3999	Single coronary vessel disease	**32627**	Type 2 diabetes mellitus with ketoacidosis

Medcode	Term	Medcode	Term
4017	Old myocardial infarction	**32671**	Chronic congestive heart failure
4024	Heart failure NOS	**32845**	[X]Depressive conduct disorder
4069	Panic disorder	**32854**	Acute posterolateral myocardial infarction
4081	[X]Panic state	**32898**	Admit heart failure emergency
4171	[X]Post - traumatic stress disorder	**32941**	[X]Recurr severe episodes/major depression+psychotic symptom
4323	Chronic depression	**32945**	Heart failure care plan discussed with patient
4634	Recurrent anxiety	**32959**	Seen in stroke clinic
4639	[X]Depressive episode	**33377**	Vertebral artery syndrome
4656	Crescendo angina	**33450**	Emphysema NOS
4659	Generalised anxiety disorder	**33469**	[X]Recurr depress disorder cur epi severe without psyc sympt
4979	[X]Postpartum depression NOS	**33499**	Pure motor lacunar syndrome
5051	Intracerebral haemorrhage	**33543**	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
5185	Lateral medullary syndrome	**34064**	[X]Phobic anxiety disorder, unspecified
5254	Double coronary vessel disease	**34135**	H/O: CVA/stroke
5255	Acute left ventricular failure	**34268**	Type 2 diabetes mellitus with neurological complications
5268	Insufficiency - basilar artery	**34328**	Refractory angina
5304	[X]Obsessive - compulsive disorder	**34390**	Single major depressive episode, unspecified
5363	CVA - cerebral artery occlusion	**34450**	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
5385	[X]Other anxiety disorders	**34633**	Other specified chronic ischaemic heart disease
5387	Other specified anterior myocardial infarction	**34758**	Cerebral embolus
5413	Coronary atherosclerosis	**34803**	Other acute myocardial infarction
5602	Cerebellar infarction	**35127**	Non-rheumatic atrial fibrillation
5678	Compulsive neurosis	**35288**	Type 1 diabetes mellitus - poor control
5710	Chronic obstructive airways disease NOS	**35385**	Type 2 diabetes mellitus with neuropathic arthropathy
5798	Chronic asthmatic bronchitis	**35671**	Recurrent major depressive episodes, unspecified
5871	H/O: stroke	**35713**	Other specified chronic ischaemic heart disease NOS
5879	Agitated depression	**36246**	Brief depressive reaction NOS
5909	Chronic wheezy bronchitis	**36423**	Certain current complication follow acute myocardial infarct
5942	Impaired left ventricular function	**36523**	Preinfarction syndrome
5987	[X] Reactive depression NOS	**36609**	Atherosclerotic cardiovascular disease
6116	CVA - Cerebrovascular accident unspecified	**36616**	[X]Monopolar depression NOS
6155	Stroke due to cerebral arterial occlusion	**36633**	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
6228	Sequelae of stroke,not specfd as h'morrhage or infarction	**36695**	Diabetes mellitus autosomal dominant type 2

Medcode	Term	Medcode	Term
6253	Stroke unspecified	**36717**	Cerebral infarction due to thrombosis of cerebral arteries
6408	[X]Panic attack	**37657**	Ventric septal defect/curr comp fol acut myocardal infarctn
6482	Recurrent depression	**37764**	[X]Recurrent severe episodes/reactive depressive psychosis
6546	Endogenous depression first episode	**37806**	Type 2 diabetes mellitus with peripheral angiopathy
6854	[X]Other depressive episodes	**37959**	Fetid chronic bronchitis
6932	Endogenous depression - recurrent	**38609**	Subsequent myocardial infarction of inferior wall
6950	Endogenous depression first episode	**38809**	[X]Other obsessive-compulsive disorders
6960	CVA - cerebrovascular accid due to intracerebral haemorrhage	**39070**	Type 1 diabetes mellitus with hypoglycaemic coma
7011	Single major depressive episode NOS	**39449**	Coronary thrombosis not resulting in myocardial infarction
7138	[V]Personal history of cerebrovascular accident (CVA)	**39481**	Metabolic syndrome X
7222	[X]Phobia NOS	**39546**	[X]Other forms of angina pectoris
7320	Ischaemic cardiomyopathy	**39655**	Impending infarction
7347	Unstable angina	**39693**	Subendocardial ischaemia
7604	[X]Single episode of reactive depression	**40159**	Purulent chronic bronchitis
7696	Syncope anginosa	**40338**	Internal capsule haemorrhage
7737	[X]Neurotic depression	**40429**	Acute anteroapical infarction
7749	[X]Mild anxiety depression	**40682**	Type 1 diabetes mellitus maturity onset
7780	Left sided CVA	**40758**	Cereb infarct due unsp occlus/stenos precerebr arteries
7884	Chron obstruct pulmonary dis wth acute exacerbation, unspec	**40788**	Other emphysema
7912	Pontine haemorrhage	**40837**	Type 1 diabetes mellitus with ketoacidotic coma
7953	[X]Dysthymia	**41221**	Acute septal infarction
7999	Anxiety counselling	**41835**	Postoperative subendocardial myocardial infarction
8205	[X]Panic disorder [episodic paroxysmal anxiety]	**41989**	[X]Single episode agitated depressn w'out psychotic symptoms
8443	Brain stem stroke syndrome	**42788**	[X]Social neurosis
8478	Reactive depressive psychosis	**42831**	Type 1 diabetes mellitus with neurological complications
8584	[X]Depressive neurosis	**43227**	Type II diabetes mellitus with multiple complications
8826	[X]SAD - Seasonal affective disorder	**43292**	Arteriosclerotic dementia with depression
8837	Cerebral arterial occlusion	**43453**	Diabetes mellitus autosomal dominant
8851	[X]Recurrent episodes of depressive reaction	**43618**	Pulmonary oedema - acute
8902	[X]Recurrent episodes of reactive depression	**43857**	Lipoatrophic diabetes mellitus
8935	Acute inferolateral infarction	**43921**	Unstable type 1 diabetes mellitus

Medcode	Term	Medcode	Term
8966	Left ventricular systolic dysfunction	**44300**	[X]Recurrent depressive disorder, unspecified
9055	[X]Single episode of depressive reaction	**44321**	[X]Other mixed anxiety disorders
9125	Anxiety management training	**44525**	Obstructive chronic bronchitis NOS
9183	Masked depression	**44765**	Carotid artery syndrome hemispheric
9211	[X]Moderate depressive episode	**44982**	Type 2 diabetes mellitus with diabetic cataract
9276	Acute coronary insufficiency	**45089**	Chronic tracheobronchitis
9386	[X]Phobic anxiety disorders	**45276**	Insulin dependent diabetes mellitus with multiple complicat
9413	Other acute and subacute ischaemic heart disease	**45809**	Subsequent myocardial infarction of anterior wall
9507	Acute non-Q wave infarction	**46017**	Other acute myocardial infarction NOS
9524	Biventricular failure	**46112**	Postoperative transmural myocardial infarction anterior wall
9555	Post infarct angina	**46166**	Subsequent myocardial infarction of unspecified site
9667	[X]Severe depressive episode without psychotic symptoms	**46276**	Postoperative transmural myocardial infarction inferior wall
9785	[X]Specific (isolated) phobias	**46301**	Type 1 diabetes mellitus with polyneuropathy
9876	Severe chronic obstructive pulmonary disease	**46316**	Basal nucleus haemorrhage
9913	Heart failure confirmed	**46578**	Panlobular emphysema
9944	Phobic anxiety	**46912**	H/O: Heart failure in last year
9985	Left sided cerebral infarction	**46917**	Type 2 diabetes mellitus with hypoglycaemic coma
10079	Right heart failure	**47009**	[X]Recurrent depress disorder cur epi severe with psyc symp
10154	Right ventricular failure	**47315**	Type II diabetes mellitus - poor control
10344	[X]Generalized anxiety disorder	**47321**	Type 2 diabetes mellitus with ophthalmic complications
10418	Type 1 diabetes mellitus with nephropathy	**47365**	Anancastic neurosis
10504	Right sided cerebral infarction	**47582**	Type 1 diabetes mellitus with renal complications
10562	Acute non-ST segment elevation myocardial infarction	**47607**	CVA - cerebrovascular accident in the puerperium
10610	Single major depressive episode	**47637**	[X]Other forms of chronic ischaemic heart disease
10667	[X]Mild depression	**47642**	Wallenberg syndrome
10692	Type 1 diabetes mellitus with ketoacidosis	**47649**	Type 1 diabetes mellitus with ophthalmic complications
10720	[X]Atypical depression	**47650**	Type 1 diabetes mellitus with multiple complications
10792	Stroke monitoring	**47731**	[X]Other recurrent depressive disorders
10794	Vertebrobasilar insufficiency	**47954**	Type 2 diabetes mellitus without complication
10802	Moderate chronic obstructive pulmonary disease	**48897**	Referral to heart failure clinic

Medcode	Term	Medcode	Term
10825	Seasonal affective disorder	**49074**	Type 2 diabetes mellitus with ulcer
10863	Mild chronic obstructive pulmonary disease	**49554**	Type 1 diabetes mellitus with diabetic cataract
10980	Centrilobular emphysema	**49655**	Type II diabetes mellitus with retinopathy
11150	Mucopurulent chronic bronchitis	**49949**	Unstable type I diabetes mellitus
11252	[X]Major depression, recurrent without psychotic symptoms	**50527**	Type II diabetes mellitus with polyneuropathy
11280	[X]Claustrophobia	**50594**	Multiple and bilateral precerebral artery syndromes
11284	Echocardiogram shows left ventricular systolic dysfunction	**51214**	New York Heart Association classification - class IV
11329	[X]Endogenous depression without psychotic symptoms	**51261**	Insulin dependent diabetes mellitus
11351	Echocardiogram shows left ventricular diastolic dysfunction	**51697**	Secondary pancreatic diabetes mellitus
11424	Compensated cardiac failure	**51756**	Type 2 diabetes mellitus with ketoacidotic coma
11602	[X]Social phobias	**51767**	Pure sensory lacunar syndrome
11717	[X]Mild depressive episode	**52517**	[X]Ischaemic heart diseases
11890	C/O - panic attack	**52678**	[X]Single episode of psychogenic depressive psychosis
11913	[X]Mixed anxiety and depressive disorder	**53392**	Type II diabetes mellitus without complication
11983	Acute coronary syndrome	**53745**	[X]Other cerebral infarction
12099	[X]Severe depressive episode with psychotic symptoms	**53810**	[X]Other intracerebral haemorrhage
12139	Acute anterolateral infarction	**54008**	Type 1 diabetes mellitus with neuropathic arthropathy
12166	Other specified chronic obstructive airways disease	**54251**	Preinfarction syndrome NOS
12229	Acute ST segment elevation myocardial infarction	**54535**	Stenocardia
12366	Congestive heart failure monitoring	**54600**	Unstable insulin dependent diabetes mellitus
12455	Type I diabetes mellitus	**54773**	Reaven's syndrome
12508	[X]Needle phobia	**55137**	MI - myocardial infarction aborted
12550	Left ventricular diastolic dysfunction	**55239**	Type 1 diabetes mellitus with gastroparesis
12590	Weak heart	**55247**	Impending cerebral ischaemia
12627	Seen in heart failure clinic	**55351**	Delivery of rehabilitation for stroke
12635	[X]Simple phobia	**56279**	Stroke in the puerperium
12640	Type 2 diabetes mellitus with nephropathy	**56458**	Ref to multidisciplinary stroke function improvement service
12736	Type 2 diabetes mellitus with gangrene	**56609**	[X]Single episode of masked depression NOS
12804	Stable angina	**56860**	Segmental bullous emphysema
12833	Right sided CVA	**57278**	Type II diabetes mellitus with renal complications
12838	Agoraphobia without mention of panic attacks	**57315**	Intracerebral haemorrhage, multiple localized
13189	New York Heart Association classification - class II	**57987**	Hyperten heartandrenal dis+both(congestv)heart and renal fail

Medcode	Term	Medcode	Term
13307	[X]Postnatal depression NOS	**59189**	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
13564	Cerebellar haemorrhage	**59253**	Type 2 diabetes mellitus with arthropathy
13566	Attack - heart	**59263**	Acute interstitial emphysema
13567	H/O: TIA	**59386**	[X]Single episode vital depression w'out psychotic symptoms
13571	Thrombosis - coronary	**59940**	Ruptur chordae tendinae/curr comp fol acute myocard infarct
13707	Stroke / transient ischaemic attack referral	**60188**	Giant bullous emphysema
14658	Acute myocardial infarction NOS	**60796**	Type II diabetes mellitus with persistent proteinuria
14709	Recurrent major depressive episodes, moderate	**61072**	Myocardial infarction aborted
14729	Phobic disorder NOS	**61118**	Simple chronic bronchitis NOS
14780	Neurotic disorder NOS	**61122**	Diabetes mellitus induced by non-steroid drugs
14798	Emphysematous bronchitis	**61430**	[X]Childhood overanxious disorder
14890	[X]Panic disorder with agoraphobia	**61513**	Mucopurulent chronic bronchitis NOS
14897	Anterior myocardial infarction NOS	**62209**	Type I diabetes mellitus with ketoacidosis
14898	Lateral myocardial infarction NOS	**62342**	Bulbar haemorrhage
15019	Cerebral embolism	**62613**	Type I diabetes mellitus without complication
15058	H/O: heart failure	**62626**	Acute papillary muscle infarction
15099	Recurrent major depressive episode	**62674**	Type 2 diabetes mellitus with mononeuropathy
15155	Single major depressive episode, moderate	**63467**	True posterior myocardial infarction
15157	Chronic bronchitis NOS	**63479**	MacLeod's unilateral emphysema
15219	Single major depressive episode, severe, without psychosis	**63521**	Antiphobic therapy
15220	[X]Persistant anxiety depression	**63690**	Type 2 diabetes mellitus with gastroparesis
15252	Brainstem infarction NOS	**64668**	Insulin treated Type II diabetes mellitus
15566	Obsessive-compulsive disorder NOS	**65267**	Type 2 diabetes mellitus with multiple complications
15626	Chronic catarrhal bronchitis	**66043**	Other chronic bronchitis
15661	Dressler's syndrome	**66145**	Type I diabetes mellitus with ketoacidotic coma
15754	Other chronic ischaemic heart disease NOS	**66306**	Heart failure as a complication of care
15788	Transient cerebral ischaemia NOS	**66388**	Status anginosus
16199	Social phobia, fear of eating in public	**66873**	H/O: Stroke in last year
16408	Healed myocardial infarction	**67040**	Other specified chronic obstructive pulmonary disease
16410	Other emphysema NOS	**67212**	DM induced by non-steroid drugs without complication
16506	Single major depressive episode, mild	**67898**	[X]Phobic state NOS
16507	Intermittent cerebral ischaemia	**67965**	[X]Acrophobia

Medcode	Term	Medcode	Term
16517	Cerebral thrombosis	**68066**	Other chronic bronchitis NOS
16632	Prolonged depressive reaction	**68105**	Type 1 diabetes mellitus with mononeuropathy
16638	Social phobic disorders	**68357**	Microinfarction of heart
16717	Smokers' cough	**68401**	[X]Other forms of acute ischaemic heart disease
16729	[X]Agoraphobia without history of panic disorder	**68662**	Zonal bullous emphysema
16861	[X]Recurrent severe episodes of psychotic depression	**68682**	Cardiac insufficiency as a complication of care
17278	Cardiac failure NOS	**68748**	Postoperative myocardial infarction, unspecified
17307	Angina at rest	**69062**	Referred by heart failure nurse specialist
17322	Cerebellar stroke syndrome	**69474**	Rupture papillary muscle/curr comp fol acute myocard infarct
17464	Personal history of myocardial infarction	**69676**	Type 1 diabetes mellitus without complication
17689	Silent myocardial infarction	**69993**	Type 1 diabetes mellitus with gangrene
17770	Psychotic reactive depression	**70619**	Referral to heart failure exercise programme
17851	Heart failure follow-up	**70779**	[X]Combat fatigue
17872	Acute anteroseptal infarction	**70787**	Atrophic (senile) emphysema
18032	[X]Separation anxiety disorder of childhood	**71235**	Referred to heart failure education group
18118	Worsening angina	**72562**	Subsequent myocardial infarction of other sites
18125	Nocturnal angina	**72702**	Insulin dependent diabetes mellitus - poor control
18248	[X]Animal phobias	**73991**	[X]Vital depression, recurrent without psychotic symptoms
18278	Insulin treated Type 2 diabetes mellitus	**83502**	Heart failure 6 month review
18387	Type 1 diabetes mellitus with retinopathy	**85991**	Type II diabetes mellitus with persistent microalbuminuria
18390	Type 2 diabetes mellitus with persistent microalbuminuria	**90572**	[X]Occlusion and stenosis of other precerebral arteries
18399	[X]Mixed obsessional thoughts and acts	**91627**	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
18425	Type 2 diabetes mellitus with polyneuropathy	**91646**	Type II diabetes mellitus with ulcer
18496	Type 2 diabetes mellitus with retinopathy	**91942**	Type I diabetes mellitus with multiple complications
18510	[X]Single episode of psychogenic depression	**91943**	Type I diabetes mellitus with polyneuropathy
18603	Social phobia, fear of public washing	**92036**	[X]Occlusion and stenosis of other cerebral arteries
18604	Stroke due to intracerebral haemorrhage	**92955**	Acute vesicular emphysema
18642	Type 1 diabetes mellitus with arthropathy	**93380**	Cystic fibrosis related diabetes mellitus

Medcode	Term	Medcode	Term
18683	Type 1 diabetes mellitus with ulcer	**93468**	Type 1 diabetes mellitus with peripheral angiopathy
18686	Stroke/CVA annual review	**93568**	Very severe chronic obstructive pulmonary disease
18689	Middle cerebral artery syndrome	**93727**	Type II diabetes mellitus with diabetic cataract
18777	Type 2 diabetes mellitus with renal complications	**93875**	Insulin dependent diabetes mellitus with retinopathy
18804	Referral to stroke clinic	**93878**	Type I diabetes mellitus with ulcer
18842	Subsequent myocardial infarction	**94383**	Secondary diabetes mellitus without complication
18853	New York Heart Association classification - class I	**94482**	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
18889	Asymptomatic coronary heart disease	**95343**	Type I diabetes mellitus with retinopathy
19000	O/E - panic attack	**95351**	Type II diabetes mellitus with mononeuropathy
19002	Seen by community heart failure nurse	**95539**	Maternally inherited diabetes mellitus
19054	[X]Recurrent brief depressive episodes	**95636**	Latent autoimmune diabetes mellitus in adult
19066	New York Heart Association classification - class III	**96076**	Persistent atrial fibrillation
19201	Right sided intracerebral haemorrhage, unspecified	**96235**	Type I diabetes mellitus maturity onset
19260	Posterior cerebral artery syndrome	**96277**	Permanent atrial fibrillation
19280	Anterior cerebral artery syndrome	**96506**	Secondary pancreatic diabetes mellitus without complication
19348	[V]Personal history of stroke	**96630**	[X]Intracerebral haemorrhage in hemisphere, unspecified
19354	Other transient cerebral ischaemia	**96799**	Post cardiac operation heart failure NOS
19655	Angina at rest	**96838**	[X]Acute transmural myocardial infarction of unspecif site
19696	[X]Recurrent episodes of psychogenic depression	**96995**	On full dose long term treatment depression - enh serv admin
20095	Angina decubitus	**97849**	Insulin dependent diabetes maturity onset
20416	Atherosclerotic heart disease	**97894**	Type I diabetes mellitus with exudative maculopathy
20634	[X]Predominantly obsessional thoughts or ruminations	**98071**	Insulin-dependent diabetes mellitus with ophthalmic comps
20773	[X]Organic anxiety disorder	**98252**	[X]Major depression, moderately severe
20785	[X]Post-schizophrenic depression	**98346**	[X]Major depression, mild
20802	Flying phobia	**98414**	[X]Major depression, severe without psychotic symptoms
20822	Congenital cardiac failure	**98417**	[X]Major depression, severe with psychotic symptoms
21061	Chronic obstruct pulmonary dis with acute lower resp infectn	**98616**	Type II diabetes mellitus with neurological complications
21118	Vertebro-basilar artery syndrome	**98704**	Insulin dependent diabetes mellitus with ulcer

Medcode	Term	Medcode	Term
21836	[X]Obsessive-compulsive neurosis	**98723**	Type II diabetes mellitus with hypoglycaemic coma
21837	Hypertensive heartandrenal dis wth (congestive) heart failure	**99311**	Type I diabetes mellitus with ophthalmic complications
21844	Transient myocardial ischaemia	**99536**	Bullous emphysema with collapse
21887	Senile dementia with depression	**99716**	Insulin dependent diabetes mellitus with hypoglycaemic coma
22116	[X]Recurrent depressive disorder, currently in remission	**99719**	Insulin-dependent diabetes without complication
22262	Rheumatic left ventricular failure	**99991**	[X]Subsequent myocardial infarction of unspecified site
22383	Other specified ischaemic heart disease	**100770**	Insulin dependent diabetes mellitus with diabetic cataract
22487	Secondary diabetes mellitus	**100964**	Type II diabetes mellitus with ophthalmic complications
22721	[X]Obsessive-compulsive disorder, unspecified	**101054**	[X]Single major depr ep, severe with psych, psych in remiss
22806	[X]Single episode major depression w'out psychotic symptoms	**101153**	[X]Recurr major depr ep, severe with psych, psych in remiss
22871	Type 1 diabetes mellitus with exudative maculopathy	**101311**	Insulin dependent diabetes mellitus with polyneuropathy
22884	Type II diabetes mellitus	**101725**	[X]Chron post-traumatic stress disorder follow military comb
23078	Chronic myocardial ischaemia	**101735**	Insulin-dependent diabetes mellitus with neurological comps
23437	Atrial fibrillation and flutter NOS	**101785**	[X]Acute post-traumatic stress disorder follow military comb
23465	Subclavian steal syndrome	**102112**	Type I diabetes mellitus with gangrene
23481	Asthma - cardiac	**102163**	Insulin dependent diabetes mellitus with nephropathy
23492	Chronic bullous emphysema NOS	**102201**	Type II diabetes mellitus with nephropathy
23566	Neonatal cardiac failure	**102620**	Type I diabetes mellitus with persistent microalbuminuria
23579	Postmyocardial infarction syndrome	**102946**	Insulin-dependent diabetes mellitus with renal complications
23618	Chronic tracheitis	**103733**	Tension pneumatocoele
23671	Cerebral infarct due to thrombosis of precerebral arteries	**103902**	Type II diabetes mellitus with arthropathy
23707	Acute congestive heart failure	**104323**	Type II diabetes mellitus with gangrene
23708	Atrial septal defect/curr comp folow acut myocardal infarct	**104608**	End stage chronic obstructive airways disease
23731	[X]Endogenous depression with psychotic symptoms	**107134**	Flooding - obsessional compulsive disorder
23838	[X]Anxiety disorder, unspecified	**108107**	Patient given advice about management of anxiety
23892	Posterior myocardial infarction NOS	**110337**	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
23942	Basilar artery syndrome	**113199**	[X]Delayed post-traumat stress disorder follow military comb

Medcode	Term	Medcode	Term
24066	[X]Other specified anxiety disorders	**114506**	Referral for guided self-help for anxiety declined
21118	Vertebro-basilar artery syndrome	**23465**	Subclavian steal syndrome
21836	[X]Obsessive-compulsive neurosis	**23481**	Asthma - cardiac
21837	Hypertensive heartandrenal dis wth (congestive) heart failure	**23492**	Chronic bullous emphysema NOS
21844	Transient myocardial ischaemia	**23566**	Neonatal cardiac failure
21887	Senile dementia with depression	**23579**	Postmyocardial infarction syndrome
22116	[X]Recurrent depressive disorder, currently in remission	**23618**	Chronic tracheitis
22262	Rheumatic left ventricular failure	**23671**	Cerebral infarct due to thrombosis of precerebral arteries
22383	Other specified ischaemic heart disease	**23707**	Acute congestive heart failure
22487	Secondary diabetes mellitus	**23708**	Atrial septal defect/curr comp folow acut myocardal infarct
22721	[X]Obsessive-compulsive disorder, unspecified	**23731**	[X]Endogenous depression with psychotic symptoms
22806	[X]Single episode major depression w'out psychotic symptoms	**23838**	[X]Anxiety disorder, unspecified
22871	Type 1 diabetes mellitus with exudative maculopathy	**23892**	Posterior myocardial infarction NOS
22884	Type II diabetes mellitus	**23942**	Basilar artery syndrome
23078	Chronic myocardial ischaemia	**24066**	[X]Other specified anxiety disorders
23437	Atrial fibrillation and flutter NOS		

Appendix XI: Mortality ICD-10 Codes

ICD-10 codes	Cause of death names
A00–R99, U00-Y89	All causes
A00–B99	I Certain infectious and parasitic diseases
A00–A09	Intestinal infectious diseases
A15–A16	Respiratory tuberculosis
A17–A19	Other tuberculosis
A39	Meningococcal infection
A40–A41	Sepsis
B15–B19	Viral hepatitis
B20–B24	Human immunodeficiency virus [HIV] disease
B90	Sequelae of tuberculosis
D50–D64	Anaemias
E00–E90	IV Endocrine, nutritional and metabolic diseases
E10–E14	Diabetes mellitus
F00–F99	V Mental and behavioural disorders
F01, F03	Vascular and unspecified dementia
F10–F19	Mental and behavioural disorders due to psychoactive substance use
G00–G99	VI Diseases of the nervous system
G00, G03	Meningitis (excluding meningococcal)
G12.2	Motor neuron disease
G20	Parkinson disease
G30	Alzheimer disease
G35	Multiple sclerosis
G40	Epilepsy
H00–H59	VII Diseases of the eye and adnexa
H60–H95	VIII Diseases of the ear and mastoid process
I00–I99	IX Diseases of the circulatory system
I05–I09	Chronic rheumatic heart diseases
I10–I15	Hypertensive diseases
I20–I25	Ischaemic heart diseases
I21–I22	Acute myocardial infarction
I26–I51	Other heart diseases
I60–I69	Cerebrovascular diseases
I60–I62	Intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I70	Atherosclerosis
I71	Aortic aneurysm and dissection
J00–J99	X Diseases of the respiratory system
J09	Influenza due to certain identified influenza virus
J10–J11	Influenza
J12–J18	Pneumonia
J40–J44	Bronchitis, emphysema and other chronic obstructive pulmonary disease
J45–J46	Asthma
K00–K93	XI Diseases of the digestive system
K25–K27	Gastric and duodenal ulcer
K40–K46	Hernia
K57	Diverticular disease of intestine
K70–K77	Diseases of the liver

L00–L99	XII Diseases of the skin and subcutaneous tissue
ICD-10 codes	**Cause of death names**
M00–M99	XIII Diseases of the musculoskeletal system and connective tissue
M05-M06, M08	Rheumatoid arthritis and juvenile arthritis
M80–M81	Osteoporosis
N00–N99	XIV Diseases of the genitourinary system
N00–N15	Glomerular and renal tubulo-interstitial diseases
N17–N19	Renal failure
N40	Hyperplasia of prostate
O00–O99	XV Pregnancy, childbirth and the puerperium
P00–P96	XVI Certain conditions originating in the perinatal period
Q00–Q99	XVII Congenital malformations, deformations and chromosomal abnormalities
Q20–Q28	Congenital malformations of the circulatory system
R00–R99	XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
R54	Senility
R95	Sudden infant death syndrome
R99	Other ill-defined and unspecified causes of mortality
S00–T98	XIX Injury, poisoning and certain other consequences of external causes
S00–S19	Injuries to the head and the neck
S20–S29	Injuries to the thorax
S30–S39	Injuries to the abdomen, lower back, lumbar spine and pelvis
S72	Fracture of femur
T20–T32	Burns and corrosions
T39.1	Poisoning by 4-Aminophenol derivatives
T40	Poisoning by narcotics and psychodysleptics [hallucinogens]
T42	Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs
T43	Poisoning by psychotropic drugs, not elsewhere classified
T50.9	Poisoning by other and unspecified drugs, medicaments and biological substances
T51–T65	Toxic effects of substances chiefly nonmedicinal as to source
T58	Toxic effect of carbon monoxide
T71	Asphyxiation
T75.1	Drowning and nonfatal submersion
V01–Y89 (inc U50.9)	XX External causes of morbidity and mortality
V01–X59	Accidents
V01–V99, Y85	Transport accidents
V01–V89	Land transport accidents
W00–W19	Falls
W65–W74	Accidental drowning and submersion
X00–X09	Exposure to smoke, fire and flames
X40–X49	Accidental poisoning by and exposure to noxious substances
X41	Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified
X44	Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
X59	Accidental exposure to unspecified factor
X60–X84	Intentional self-harm
X85–Y09	Assault
Y10–Y34	Event of undetermined intent
X60–X84, Y10–Y341	Intentional self-harm; and event of undetermined intent

U50.9, X85–Y091	Assault; death from injury or poisoning, event awaiting determination of intent (inquest adjourned)