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Evaluation of opioid-related deaths associated with opioid utilisation and the impacts of tramadol classification as a Schedule III Controlled Drug in the United Kingdom

Thesis submitted to the University of Nottingham for the degree of

Doctor of Philosophy

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Dedication

For my parents and brother.

Abstract

In the past two decades, there has been a marked increase in opioid utilisation paralleled with the rising opioid mortality in many western countries. In contrast to opioid-overdose deaths in the United States which were mainly caused by opioid poisoning, the increasing opioid-related death in the United Kingdom (UK) involves a complex mechanism, including persistent opioid utilisation, medicines for chronic pain management and illicit drugs. However, no research has evaluated the association between opioid-related death, opioid utilisation and other determinants in the UK. In June 2014, tramadol was classified as a Schedule III controlled drug due to the concerns of increasing tramadol utilisation and tramadol-related deaths, but no research has evaluated the impact of the tramadol classification.

Therefore, this PhD project aimed to identify the association between opioid utilisation and opioid-related deaths in the UK primary care setting and to evaluate the impact of policy implementation using tramadol as a case study.

This study took a drug utilisation research and pharmacoepidemiology approach to develop and test a hypothesis about the association between opioid-related deaths and opioid utilisation. Firstly, a cross-sectional study was conducted using the UK Clinical Practice Research Datalink and aggregate-level national data to evaluate the impact of tramadol classification on tramadol utilisation, the prevalence of tramadol users and tramadol-related deaths by interrupted time-series analysis. Secondly, a case cross-over study was conducted to identify cases of opioid-related death, explore the characteristics and medication utilisation of opioid-related deaths and investigate the association between opioid-related death and opioid daily dose. Finally, a nested case-control study was conducted to analyse the association between opioid-related death and persistent opioid utilisation in the three patient-years retrospectively followed from the date of opioid-related deaths by conditional logistic regression.

After tramadol classification, the levels of monthly tramadol utilisation and the prevalence of tramadol users decreased by 12.9 defined daily dose/1000 registrants and 6.4 tramadol users/10000 registrants. In

addition, the trends of monthly tramadol utilisation and the prevalence of tramadol users decreased by 1.6 defined daily dose/1000 registrants and 0.37 tramadol users/10000 registrants. The impacts of tramadol classification seems predominantly associated with the reduced accessibility of tramadol to both new and existing users. Of the 232 cases of opioid-related deaths, 62 (26.7%) cases did not receive any opioid in the one year before opioid-related death. Only 48 cases received a daily dose of opioid of more than 120 mg oral morphine equivalent (OMEQ) dose in the final year, and an opioid daily dose more than 120 mg OMEQ dose was not significantly associated with opioid-related deaths (adjusted odds ratios [aOR]: 1.4; 95% confidence interval [95%CI]: 0.52, 3.6). In addition, most of the opioid-related deaths were diagnosed with alcohol abuse disorders (25.4%), other substance abuse disorder (30.6%), had a history of overdose of any medication (26.7%) or were regularly prescribed with sedatives (81%). Compared to patients who were not prescribed with opioids persistently, persistent opioid use in any of the last three retrospective patient-years was associated with an increased risk of opioid-related death (aOR: 2.0; 95%CI: 1.3, 3.1), especially in the final retrospective patient-year (aOR:

3.6; 95%CI: 1.6, 8.0). In addition, a higher risk of opioid-related death was observed when taking a higher dose of benzodiazepines, gabapentin/pregabalin and tricyclic antidepressants.

This is the first study applying nationwide individual patient data and aggregate-level national data to evaluate the impact of tramadol classification and the association between opioid-related deaths and opioid utilisation in the UK. Tramadol classification reduced the increasing tramadol prescribing and tramadol-related deaths in a short term, but the impacts on the utilisation of other medications with abuse potential and the effectiveness of chronic pain management among individual patients are still unclear. In addition to substance abuse and concurrent sedatives, opioid-related deaths are associated with persistent opioid utilisation. As the effectiveness of persistent opioid utilisation is not supported by published evidence and persistent opioid utilisation is related to opioid related death in this study, an information system longitudinally evaluating the benefits and risks of opioid treatment for individual patients may be beneficial to facilitate opioid deprescribing. Further studies need to investigate the optimisation of

opioids for patients with chronic pain and attitude of opioid disposal and diversion from potential prescribing opioid abusers.

List of publications

Peer reviewed journals

Teng-Chou Chen, Li-Chia Chen and Roger Knaggs. A fifteen-year overview of increasing tramadol utilisation and associated deaths and the impact of tramadol classification in the UK. Pharmacoepidemiology and Drug Safety 2017; 1-8. (Chapter 3)

Teng-Chou Chen, Li-Chia Chen and Roger Knaggs. Identifying patterns of persistent tramadol utilisation using a multiple-dimension algorithm to longitudinal prescribing data in the United Kingdom. (Chapter 4) to be submitted to *British Journal of General Practice*

Conference presentations

1. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Association between persistent opioid prescribing and opioid-related deaths in the United Kingdom. **Poster presentation**. 2018 International Society of Pharmacoepidemiology ISPE meeting, 22 to 26 August 2018 at Prague, Czech Republic.

2. Hsin-Te Lin, Teng-Chou Chen, Li-Chia Chen. Measuring opioid utilisation for chronic non-cancer pain: A systematic review. **Poster presentation**. 2018 International Society of Pharmacoepidemiology ISPE meeting, 22 to 26 August 2018 at Prague, Czech Republic.

3. Jessica Jia Li, Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Variation in observational studies exploring long-term opioid effectiveness in chronic non-cancer pain - a systematic review. **Poster presentation- Best poster presentation.** 10th Congress of the European Federation of Pain, EFIC. 6 to 9 September 2017 at Copenhagen, Denmark.

4. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Tramadol classification had no impact on other opioids utilisation in England. **Podium presentation**. 2017 International Society of Pharmacoepidemiology ISPE meeting, 26 to 30 August 2017 at Montreal, Canada. Pharmacoepidemiol Drug Saf, 26: 3–636.

5. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. A close link between opioid related mortality and medicines commonly used for chronic pain. **Podium presentation**. 2017 International Society of Pharmacoepidemiology ISPE meeting, 26 to 30 August 2017 at

Montreal, Canada. Pharmacoepidemiol Drug Saf, 26: 3–636.

6. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. The impact of classification as a Controlled Substance on tramadol utilisation in the United Kingdom. **Poster presentation**. 2017 International Society of Pharmacoepidemiology Mid-year ISPE meeting, Royal College of London, 3 April 2017.

7. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Patient characteristics associated with persistent tramadol use for patients with chronic non-cancer pain in U.K. general practices. **Spotlight Poster- Spotlight Poster Winner**. The 32nd Anniversary International Conference on Pharmacoepidemiology and Therapeutic Risk Management, 25-28 August 2016 at the Convention Center Dublin, Dublin, Ireland. Pharmacoepidmiology and Drug Safety, 2016;25(S3): 293.

8. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. The difference in baseline characteristics between persistent tramadol users defined by different criteria. **Poster presentation**. The 32nd Anniversary International Conference on Pharmacoepidemiology and Therapeutic Risk Management, 25-28 August 2016 at the

Convention Center Dublin, Dublin, Ireland. Pharmacoepidmiology and Drug Safety, 2016;25(S3): 218

9. Joyce Wang, Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. The influence of concomitant opioids on opioid utilisation for tramadol users – a retrospective cohort study in the UK primary care setting. **Poster presentation**. The 32nd Anniversary International Conference on Pharmacoepidemiology and Therapeutic Risk Management, 25-28 August 2016 at the Convention Center Dublin, Dublin, Ireland. Pharmacoepidmiology and Drug Safety, 2016;25(S3): 218

10. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Tramadol used for Chronic Pain Management. **Podium presentation**. University research Showcase 2016, A16 Atrium Engineering and Science Learning Centre University Park Campus, 15 June 2016.

11. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Patient characteristics associated with persistent tramadol use for patients with chronic non-cancer pain in U.K. general practices. **Podium presentation**. LINK 16, East Midlands Conference Centre, 3 June 2016.

12. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Defining persistent tramadol utilization using a multiple-dimension algorithm - a cohort study in the United Kingdom primary care setting. **Podium presentation**. 2016 Health Service research and Pharmacy Practice Conference, 7-8 April 2016, University of Reading, UK. International Journal of Pharmacy Practice. 2016;24(Suppl 1):25.

13. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Evaluation of safety outcomes associated with persistent tramadol utilisation in patients with chronic non-cancer pain. **Podium presentation**. 2015 Taiwan Scientific Symposium, Manchester, UK, December 2015.

14. Teng-Chou Chen, Li-Chia Chen, Roger Knaggs. Prevalence of antidepressants prescribed to tramadol users in the UK primary care setting - a prescription sequence symmetry analysis. **Poster presentation**. The ISPOR 18th Annual European Congress, 10 November 2015, MiCo-Milano Congressi in Milan, Italy. Value Health. 2015 Nov;18(7):A661.

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16. Teng-Chou Chen, Jodie Fisher, Li-Chia Chen, Roger Knaggs. Prevalence of antidepressants prescribed to tramadol users in the UK primary care setting - A prescription sequence symmetry analysis. **Poster presentation**. Practice Innovation Showcase. Royal Pharmaceutical Society Annual Conference 2015, Birmingham, 13 September 2015. International Journal of Pharmacy Practice. 2015;23(Suppl 2): 23-106.

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List of abbreviations

95%CI	95% confidence interval
ACMD	Advisory Council on the Misuse of Drugs
ACTTION	Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks
AD	Annual dose
aOR	Adjusted odds ratio
BNF	British National Formulary
BSA	Business Services Authority
BZDs	Benzodiazepines
CDC	Centers for Disease Control and Prevention
CLR	Conditional logistic regression
CNCP	Chronic non-cancer pain
CNS	Central nervous system
CONSORT	Consortium to Study Opioid Risks and Trends
COM-B system	Capability, opportunity, and motivation behaviour system
COX-2	Cyclooxygenase 2
CPRD	Clinical Practice Research Datalink
CPRP	Comprehensive pain rehabilitation programs
CROP	Campaign to Reduce Opioid Prescribing
CYP2D6	Cytochrome P450 isoenzyme 2D6
DDD	Defined Daily Dose
DSM-5	The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders
FDA	Food and Drug Administration
HES	Hospital Episode Statistics
ICD-10	International Classification of Diseases- the tenth version

IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
INCB	International Narcotics Control Board
IPD	Individual patient data
ITSA	Interrupted time-series analysis
I-WOTCH	Improving the Wellbeing of People with Opioid Treated Chronic Pain
MDA	Multiple-dimension algorithm
MDD	Mean daily dose
NCIS	National Coronial Information System
NDTMS	National Drug Treatment Monitoring System
NHS	National Health Service
NNH	Number needed to harm
NP	Annual number of prescription
NQC	Annual number of quarters covered with prescription
NSAIDs	Nonsteroidal anti-inflammatory drugs
OMEQ	Oral morphine equivalent
ONS	Office for National Statistics
OR	Odds ratio
PCA	Prescription Cost Analysis
PDMP	Prescription Drug Monitoring Program
PTSD	Post-traumatic stress disorder
RACCDMU	Review and Approval Committee on Controlled Drugs for Medical Use
RCTs	Randomised controlled trials
Ref	Reference
RON	Registration Online system
SD	Standard deviation
SES	Socioeconomic status

SNRI	Serotonin norepinephrine reuptake inhibitors
SR	Systematic review
SSRI	Selective serotonin reuptake inhibitor
TCAs	Tricyclic antidepressants
TFDA	Taiwan Food and Drug Administration
THIN	The Health Improvement Network
TROUP	Trends and Risks of Opioid Use for Pain
UK	United Kingdom
uOR	Unadjusted odds ratio
US	United States
WHO	World Health Organisation

Chapter 1. Introduction

1.1. Background

This PhD research focused on safety and optimisation of opioid use, in particular, the long-term use of opioids in patients with chronic non-cancer pain (CNCP). It was motived by the recent change in controlled United Kingdom (UK) drug regulations related to prescribing of tramadol and by the 'opioid epidemic', the increase in opioid overdose deaths in North America, Australia and European countries. As opioid-related harms involve a complex mechanism, a pharmacoepidemiologic approach, including hypothesis developing and testing, was taken to evaluate the association between opioid use and related harms in the UK.

Opioids are potent analgesics and traditionally used for cancer pain or short-term postoperative pain as they were recommended by the World Health Organisation (WHO) analgesic ladder[1]. However, in the past two decades, there is a marked and persistent increase in opioid utilisation in western countries, predominantly due to the persistent use of opioids for CNCP[2].

The persistent use of opioids for CNCP is still controversial due to a lack of robust evidence-based knowledge regarding the effectiveness of long-term opioid utilisation[3-5]. In contrast, persistent opioid utilisation has been found to be associated with increased risks of adverse effects, emergency department visits, addiction, tolerance, dependency and mortality[6-9]. In addition, central nervous system (CNS) depressants for managing common symptoms of chronic pain, such as depression, anxiety and insomnia are often concurrently prescribed with opioids[10-12] and lead to the increased risk of over-sedation, overdose and mortality[13, 14].

A classic example to illustrate opioid related safety issue is in the United States (US). The increase in prescribed opioids has accounted for most of the increase in opioid overdose deaths from 2000[15-18], and the use of high-dose opioids is the main reason for opioid overdose death in the US[19]. In 2017, the opioid crisis has been declared as a national public health emergency by the US President and has linked to a two-year drop of life-expectancy in the US[20]. Therefore, consistent with the previous

US public health strategy (Healthy People 2010), reducing opioid overdose death is prioritised as one of the Healthy People 2020 objectives[21].

Compared to the increased number of 'opioid overdose deaths' in the US, which was mainly caused by overdose of opioids, the increase of 'opioid-related deaths' in the UK reveals a complex mechanism related to inadequate management of chronic pain and persistent opioid utilisation[22-24]. Driven by the increased number of people using heroin from 1980, the number of drug misuse deaths increased from 1990 in the UK[25]. After that, the number of opioid-related deaths slightly decreased between 2010 and 2012 due to a 'heroin drought', which means the decreased availability and purity of heroin at street level due to crop failures in the Afghan poppy fields and conflict in Pakistan and Afghanistan[26, 27], but increased 54.2% from 2012 to 2015 in England and Wales; and this pattern paralleled with the increase of persistent opioid prescriptions for patients with chronic pain[25, 28, 29]. Optimising use of prescription opioids in patients with CNCP has become an emerging issue in North American, European countries and Australia, and a

variety of strategies and policies have been implemented[30]. In particular, the change to controlled drug regulations of tramadol in the UK intrigued the research motivation of this PhD project.

Tramadol is a synthetic analogue of codeine with a dual pharmacologic mechanism[31], and traditionally considered relatively safe compared to other strong opioids[32]. In line with the increased utilisation of other prescription opioids in the UK, data from the National Health Service (NHS) Business Services Authority (BSA) showed that the number of defined daily dose (DDD) of tramadol consumption almost doubled from 2005 to 2012[33]. However, in contrast to the reduction in the number of opioid-related deaths between 2010 and 2012[25, 28, 34], the number of opioid-related deaths involving tramadol increased from 87 in 2009 to 154 in 2011, and there were a total of 1347 tramadol-related deaths up to 2014 according to death certificate[28].

In response to the increasing number of deaths involving tramadol, the classification of tramadol was changed in Sweden in 2012[35] and America in 2014[36]. Likewise, concerns about the safety and potential

risks of misuse and dependence of tramadol, tramadol was classified as a Schedule III Controlled Drug in the UK from June 2014[33]. However, the reasons attributable to the increasing tramadol utilisation have not been investigated, and the effectiveness of such a policy intervention on utilisation and tramadol-involved opioid-related deaths has not been explored. The limited accessibility of tramadol might switch the use of tramadol to alternative stronger opioids for achieving good pain relief.

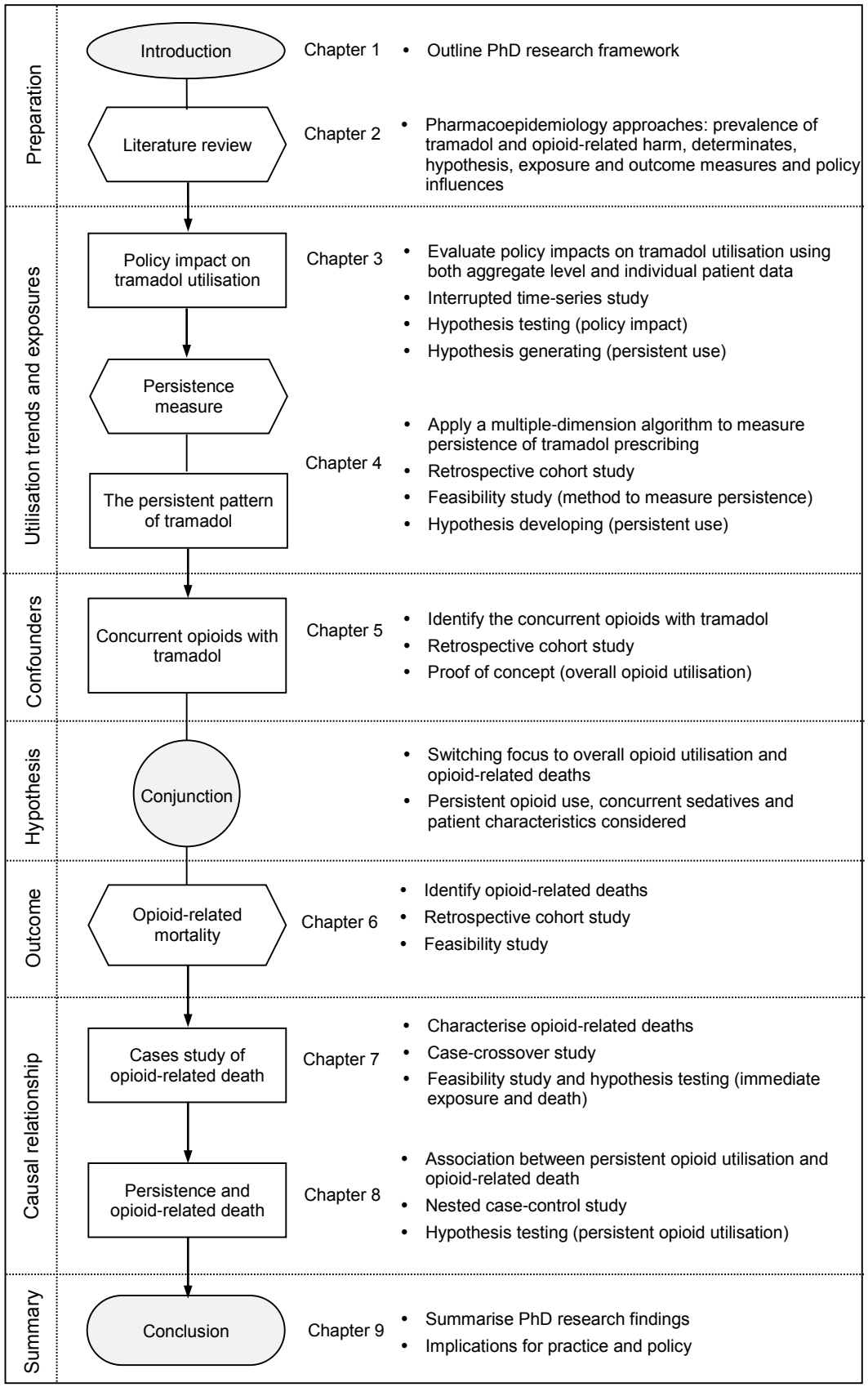
A case review conducted in Northern Ireland reported that more than half of tramadol-related fatalities were persistent tramadol users, as most of them had been diagnosed with chronic pain and prescribed tramadol in combination with other opioids and benzodiazepines (BZDs)[37]. However, epidemiology studies evaluating the safety of persistent opioid utilisation were also lacking in the UK. Furthermore, published statistics about the increased opioid use and opioid-related deaths from the UK Office for National Statistics (ONS) are based on aggregate-level population data[25, 28, 33, 38]. Therefore, individual patients' characteristics, opioid utilisation and its association with opioid-related deaths were unclear in the UK.

Due to the discrepancy in outcome definitions between different countries (e.g. opioid-overdose death in the US and opioid-related death in the UK) and the different mechanisms causing opioid-related harms, the evidence to infer safety associated with opioid utilisation need to be interpreted with caution. The evidence from epidemiology studies exploring opioid dose and related harms to inform prescribing guidance in the US[5] may not be directly applicable to the same situation in the UK. To optimise the use of long-term opioid for patients with chronic pain and inform evidence-based practice and future policy implementation, pharmacoepidemiological evaluations on tramadol classification, opioid utilisation pattern and safety outcomes associated with persistent opioid utilisation are needed.

Therefore, this PhD research adopted an epidemiological approach to (1) evaluate the impacts of tramadol classification as a controlled drug, (2) unpack opioid related safety issues from describing persistent opioid utilisation and (3) explore its association with opioid-related mortality in the UK by using secondary healthcare databases. The PhD research

framework involved both hypothesis developing and testing processes, and the PhD thesis is divided into nine chapters (Figure 1).

Figure 1. Conceptual framework and thesis development process



1.2. Preliminary work – literature review

First of all, in order to support the rationale of this PhD project, a comprehensive literature review (Chapter 2) was conducted to summarise current evidence and identify knowledge gaps. This chapter summarises the evidence regarding increasing opioid utilisation and its association with prolonged opioid use in western countries and highlights the controversy of persistent use of opioids due to lack of efficacy and safety concerns. In addition, according to published epidemiologic studies and government reports, the difference in epidemiology statistics, patients' characteristics and medication utilisation between opioid-overdose deaths in the US and opioid-related deaths in the UK is presented to highlight the needed of UK-based evaluation on opioid-related deaths. Finally, the mechanism of tramadol-related serious adverse events and the regulation of tramadol classification are described.

1.3. Drug utilisation research – both aggregate and individual levels

The first part of this PhD study was drug utilisation research including a

case study to assess the impact of classifying tramadol as a controlled drug (Chapter 3), a feasibility study to quantify the patterns of persistent tramadol utilisation (Chapter 4), and the combination of tramadol and other opioids (Chapter 5).

A segmented regression analysis of the interrupted time-series study was conducted using the UK aggregate-level national statistics and prescribing reimbursement data to understand the trends of tramadol-related deaths and tramadol utilisation in the past decade and to evaluate the impact of tramadol classification. In addition to the impact of tramadol classification, possible reasons for increasing tramadol utilisation were also explored by using individual patient data (IPD) from the UK Clinical Practice Research Datalink (CPRD) (Chapter 3). In this time-series study, the increasing tramadol utilisation was found to be associated with the increasing prevalence of tramadol users, mean daily dose and days of supply. This result motived the further work exploring the association between persistent tramadol use and its associated deaths.

To explore issues related to persistent tramadol use, a retrospective cohort study using the CPRD was conducted to investigate the feasibility of the methodology to quantify and define persistent tramadol utilisation. Persistent tramadol utilisation was identified using a multiple-dimension algorithm (MDA), which was also applied to measure the persistence of opioid exposure in the published literature[39]. Also, the association between baseline patient characteristics (before tramadol initiation) and persistent tramadol utilisation were also investigated (Chapter 4).

In this feasibility study, the recurrent pattern of persistent tramadol utilisation was found, which is similar to persistent opioid utilisation reported in previous publications[39, 40]. Also, some conditions at baseline, such as common psychological co-morbidities and medications for CNCP, such as other opioids and BZDs were found associated with persistent tramadol utilisation. However, most of those factors are the common comorbidities or pharmacotherapies for patients with CNCP. Previous literature has found an association between higher opioid dose and the diagnosis of common psychological illnesses and substance abuse disorders among persistent opioid users[6, 40], which also contribute

to opioid-related deaths and other serious adverse events[9, 25, 41-44]. Therefore, an exploratory study was conducted to understand the combination of opioids and sedatives.

The exploratory study was a two-stage process. Firstly, tramadol users were categorised into persistent and non-persistent tramadol users by using the MDA and followed from tramadol initiation to measure utilisation of other opioids (Chapter 5). The results revealed that non-persistent tramadol users were prescribed other opioids with a higher dose and longer duration than persistent tramadol users. As there is a dose-response relationship for the majority of serious opioid-related adverse events, this indicates that to explore the determinants of opioid-related deaths, it is necessary to treat opioids as a class rather than only measure the exposure of a single opioid, such as tramadol.

Secondly, to understand the prevalence and utilisation of concurrent sedatives with opioids, opioids users were categorised as persistent and non-persistent opioid users by using the MDA, and the use of concurrent sedatives was quantified (Chapter 5). The results showed a higher

proportion of persistent opioid users were concurrently prescribed opioids with sedatives, and higher dose and longer duration of concurrent sedatives were also found among persistent opioid users. Overall, this study which explored persistent opioid exposure and concurrent sedatives intrigued the further studies exploring the determinants of opioid-related deaths.

1.4. Pharmacoepidemiology research – explore the causality

The second part of this PhD project aimed to explore the association between opioid utilisation and opioid-related deaths. This part concluded that the majority of opioid-related deaths in the UK received opioids with a low dose for an extend period and persistent opioid utilisation was associated with opioid-related deaths.

As the CPRD provides longitudinal prescription data and the ONS death registration included all deaths occurring in England and Wales, the linkage between these two datasets offer necessary information for this project. However, the feasibility of applying published methods to

identify opioid-related deaths or rare and serious adverse events, e.g. tramadol-related seizure or serotonin syndrome, were still unclear. Therefore, a retrospective cohort study was conducted using CPRD linked with Hospital Episode Statistics (HES) and ONS death certification (Chapter 6) to investigate the feasibility of methodology to identify serious opioid-related safety outcomes. Based on the estimated incidence of identified events and the demographic distribution, published methods were applied in the databases to identify opioid-related deaths and tramadol-related serious adverse events. Therefore, the next two chapters focused on the evaluation of opioid-related deaths and tested the potential hypothesis of the relationship between opioid utilisation and opioid-related death.

Although the mean daily opioid dose during a short period of time (0 to 90 days) before an event occurred was related to opioid-overdose deaths in the North America[7, 9, 41, 42, 45], there has been no research applying individual-patient data to explore patients' characteristics, medication utilisation and the association between mean daily opioid dose and opioid-related deaths in the UK. Therefore, a case-crossover

study (Chapter 7) was conducted to explore characteristics and medication utilisation associated with opioid-related deaths and hypothesised that a high opioid dose during a short period before death was associated with the increased risk of opioid-related death in the UK.

The results of this case-crossover study showed that most cases of opioid-related deaths were prescribed opioids for a long period, but more than 80% of deaths never been prescribed opioids at mean daily dose more than 120 mg oral morphine equivalent (OMEQ) dose during the final year of their life. The non-significant association between transient opioid dose increase and opioid-related deaths implied that persistent opioid utilisation and potential abuse and misuse need to be considered to infer the association.

Therefore, a nested case-control study was conducted to evaluate the association between persistent opioid utilisation and opioid-related deaths after adjusting for concurrent prescribing of sedatives (Chapter 8). The results showed that persistent opioid utilisation in any of the three patient-years before death was associated with an increased risk of

opioid-related death. Especially persistent opioid utilisation in the final year was associated with the highest risk of opioid-related death when compared to non-persistent opioid users after adjusting for concurrent sedatives. In addition to persistent opioid utilisation, taking a higher dose of BZD and gabapentin/pregabalin was consistently associated with a higher risk of opioid-related death in the UK.

Finally, the reasons driving increased opioid utilisation in the UK and determinants related to opioid-related deaths are summarised. The strengths and limitations of the research conducted in this PhD project are considered, together with implications for clinical practice. Further policy implementation and recommendations for future studies are also summarised in Chapter 9.

Chapter 2. Literature review

2.1. Introduction

To summarise current knowledge gaps regarding the association between persistent opioid utilisation and effectiveness and safety for patients with CNCP, this literature review chapter depicts the challenging issues associated with persistent opioid utilisation which underpins the increasing trend of opioid utilisation in the past two decades. In addition, challenges about lacking evidence-based efficacy and concerns on the safety of persistent opioid utilisation for patients with CNCP are also summarised in this chapter.

The pharmacoepidemiological evidence derived from both aggregate and individual-patient healthcare data around the association between increasing opioid utilisation and opioid-overdose deaths in the US and its potential determinants are retrieved and critiqued. In contrast, the data from official statistics, epidemiologic studies and government reports about opioid-related deaths in the UK are presented and compared with US data. Due to discrepancies in medication utilisation and outcome definition, the challenges of applying the evidence from the

US to the UK practice environment are summarised to address the needs of UK-based evaluation around opioid-related safety.

In order to apply tramadol as a case study to evaluate the effectiveness of policy implementation in increasing tramadol prescribing and tramadol-related death, the official UK statistics for tramadol prescribing and tramadol-related deaths and the subsequent policy of tramadol classification as a controlled drug are described to provide the background context. Existing pharmacoepidemiology studies exploring the association between tramadol-related serious adverse events and tramadol utilisation were reviewed to explore the possible mechanisms associated with tramadol-related deaths.

The evidence gaps identified from literature review, including factors underpinning the increasing trend of tramadol and opioid utilisation, the association between increased opioid utilisation and opioid-related deaths and effectiveness of policy implementation on tramadol prescribing and tramadol-related death explain the need for further studies.

2.2. Increasing opioid utilisation in Western countries

Historically, ‘opium’ refers to a mixture of alkaloids extracted from the poppy seed which have been used for more than thousands of years because of its pain-relieving property[46] whilst the term ‘opiate’ is used to describe drugs derived from the juice of the opium poppy and natural alkaloids (e.g. morphine or codeine) and semi-synthetic opioids created from either the natural alkaloids or morphine esters (e.g. hydromorphone, hydrocodone, oxycodone and buprenorphine)[47]. Other opioids (e.g. methadone, tramadol, fentanyl, pethidine, tapentadol and dextropropoxyphene) have no structural similarity to morphine and are referred to as ‘synthetic opioids’[47].

In general, ‘opioid’ is used to describe all natural and synthetic compounds that work at opioid receptors[48], but have various pharmacological mechanisms, metabolic pathways, active metabolites and formulations[49, 50]. According to the affinity to μ opioid receptors and the tendency to cause dependency, opioids are generally categorised into weak and strong opioids[48, 50].

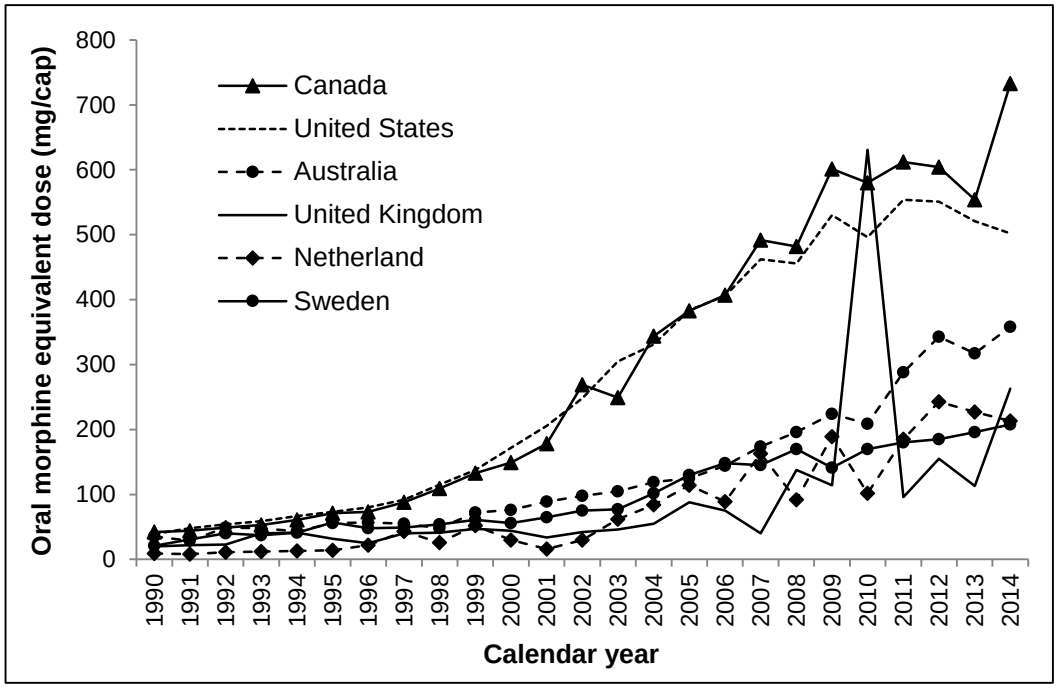
Traditionally, opioid analgesics were used for cancer pain as recommended by the WHO analgesic ladder or short-term postoperative pain[1]. Under the notion that pain relief is a human right, opioid consumption in individual countries has been considered as an essential indicator of cancer pain relief by WHO[51]. To promote the accessibility of opioids, a list of potent opioids including morphine, fentanyl, oxycodone, hydromorphone and methadone were included in the WHO Model Lists of Essential Medicines[52]. However, the dilemma of using opioids in pain management needs to balance the benefits of pain control and the risks of potential harms, in particular, the serious adverse events, e.g. respiratory depression, euphoria, sedation and dependence[48].

Therefore, according to the Single Convention on Narcotic Drugs 1961 (which was expanded and strengthened by the 1972 Protocol), WHO member countries report the statistics of total amount of opioids distributed for medical purposes annually to the International Narcotics Control Board (INCB) to monitor and limit the use, trade in, distribution and production of opioids exclusively to medical and scientific purposes in those institutions that are licensed to dispense[53]. This initiative

generated a series of trend data for monitoring opioid utilisation cross-nationally and, it has been used to evaluate the impacts of WHO's guidance on cancer pain management.

For example, to monitor the access to opioids for managing cancer pain, the WHO Pain and Policy Studies Group applied the INCB data of several potent opioids that are commonly used for cancer pain and adjusted for the population size of individual countries to derive the annual trend of OMEQ dose/ capita (Figure 2)[54]. The trend demonstrates an increased consumption of those strong opioids in North America, Australia and European countries after the WHO published the three-step analgesic ladder for cancer pain relief in 1986 [55, 56], which implies an increased use of strong opioids in patients with cancer pain.

Figure 2. Strong opioid consumption in North America, Australia and European countries



(Note) This figure is generated by applying data published on the WHO Pain and Policy Studies Group website[55].

In addition to the WHO's initiative in promoting the use of opioids to improve management of cancer pain, several organisations (e.g. the American Society of Anaesthesiologists, the American Academy of Pain Medicine and the American Pain Society) published guidance in 1990s[57-59] and recommend prescribing opioids to achieve better management of CNCP. These guidelines might influence prescribers' attitude and cause the increased use of opioids for patients with

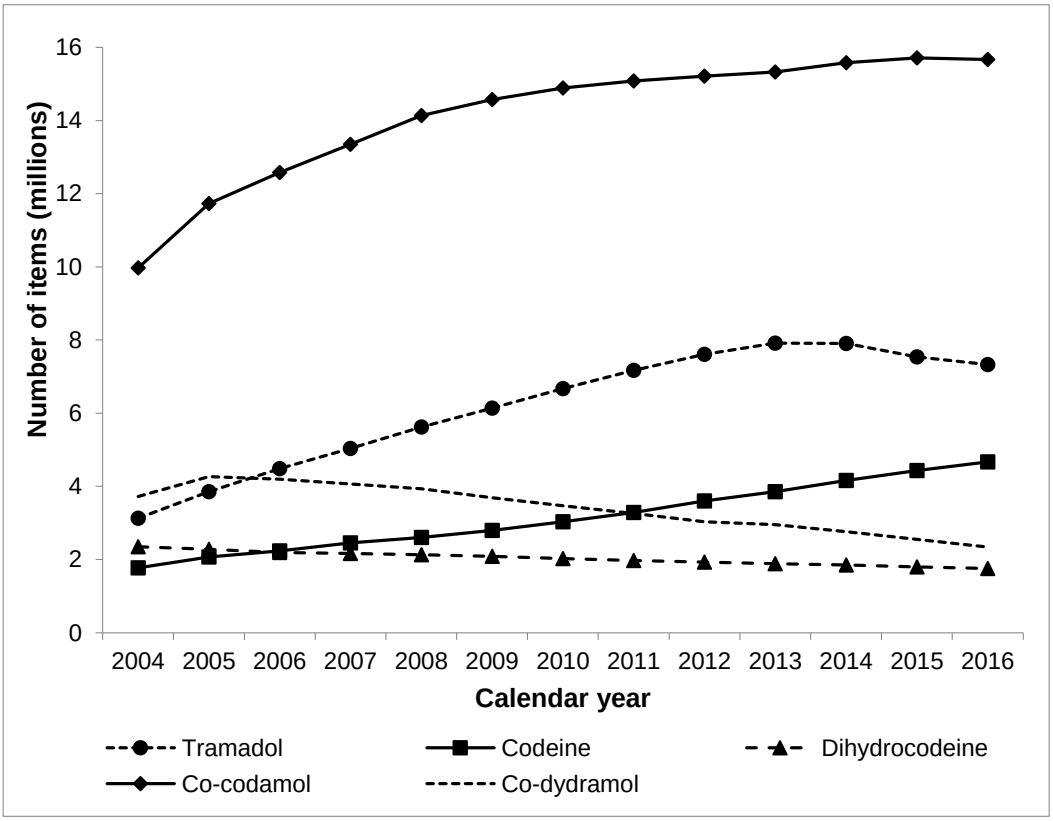
CNCP[60].

DDD is the average daily maintenance dose for a drug used for its main indication in adults and is often applied to quantify medications use in individual countries[61]. Berterame *et al.* (2016) applied the INCB data from 214 countries to calculate the total consumption of opioids in the numbers of DDD per million inhabitants per day during two periods, i.e. 2001 to 2003 and 2011 to 2013. In addition to the opioids monitored by Pain and Policy Studies Group, some less potent opioids (i.e. codeine, dextropropoxyphene, dihydrocodeine, hydrocodone, ketobemidone, tilidine, and trimeperidine) were also included. Overall, the total consumption of opioids increased more than twice from 2001-2003 to 2011-2013, and the largest increase was found in North America, western and central Europe and Oceania[62]. This evidence indirectly implies that there was an increasing trend in weak opioid consumption.

In the UK, opioid analgesics are recommended for cancer pain or short-term postoperative pain. Similar to the trends found in other western countries, the consumption of strong opioids in the UK also

increased over time. In addition to strong opioids, according to the data published by the NHS Digital, annual quantity (items) of dispensed weak opioids preparations also increased steadily from 2004 (Figure 3), and tramadol and codeine became the most frequently prescribed opioids in England up to 2016[63].

Figure 3. Annual quantity of dispensed tramadol, dihydrocodeine and codeine preparations between 2004 and 2016 in England



(Note) This figure is generated by applying data published on the NHS Digital website[63].

2.3. Chronic non-cancer pain and increasing opioid utilisation

CNCP is generally defined as either pain persists beyond the expected time of tissue healing or pain persisting for at least three to six months[64-66]. CNCP is a common condition in the general population, and the estimated prevalence of CNCP in western countries varies between 18% and 33% according to studies conducted by different methods, such as postal, telephone or face-to-face interview[67]. A systematic review (SR) summarised epidemiology data of CNCP and found that the estimated prevalence ranged from 2.9% to 17.1% according to different pain conditions, such as low-back pain, arthritis and neuropathic pain once ask patients whether there is any pain in the past one month, and the estimated one-month prevalence of moderate-to-severe CNCP was 19% in Europe[68]. In the UK, the life-long prevalence of CNCP in the community was estimated as 50.4% according to a postal self-completion questionnaire survey conducted in the 29 general practices in the Grampian region of Scotland, and this is equivalent to 46.5% of the general population. Of patients with self-reported CNCP, 48.3% had the least severe grade of pain and 15.8% had the most severe grade[69].

CNCP not only causes detrimental impacts on individual patients' physical activity, mental health, physical function, quality of life but also results in an enormous disease burden on the society[10, 70-72]. A retrospective cohort study used the UK CPRD to access health care resource use for patients with chronic low back pain, and found the total health care resource use for patients with chronic low back pain in the first 12 months after diagnosis was twice more than the general population who matched on age and gender on the index date[73]. Despite the huge disease burden associated with CNCP, globally, the quality of pain control is still suboptimal. Therefore, improving pain management is regarded as a public health priority in many countries. The Veterans Health Administration in the US called for the "Pain as the 5th Vital Sign" initiative in 1999 for the better management of pain [74]. To achieve better pain management for CNCP, the Chief Medical Officers Report in 2008 also highlighted pain management for CNCP as the primary healthcare priority in the UK[75].

A US web-based survey identified relevant domains of patient-reported outcomes from almost 1000 patients with CNCP, in addition to pain

reduction, quality of life, functional improvement, emotional well-being and sleep-related problem were identified as main target domains in the management of CNCP[76]. To manage symptoms and improve physical, social and emotional function associated with chronic pain, a multidisciplinary approach, including surgery, rehabilitation and psychological intervention and pharmacotherapy has been recommended by the American Pain Society and American College of Physicians[77, 78].

Pharmacotherapy is the main treatment strategy for controlling the symptoms of CNCP, and several medications, such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, anti-epileptic, antidepressants and opioids have been recommended in treatment guidance[77, 78]. NSAIDs and paracetamol are recommended as the first line therapy for mild to moderate pain, but they only have a mild effect on chronic pain control and paracetamol has no effect on functional improvement[79, 80]. In fact, paracetamol alone was not recommended for low back pain in updated guidance from the National Institute for Health and Care Excellence in

the UK in 2016[81]. The use of NSAIDs and COX-2 inhibitors in patients with CNCP is limited by the concerns on potential cardiovascular and gastrointestinal events [82, 83]. Opioids are generally regarded as second-line treatments for CNCP due to worries on dependence, tolerance and addiction[1, 6]. However, increasing opioid utilisation in the majority of western countries has been associated with the use of opioids for patients with CNCP.

In the US, drug utilisation research [2, 84-86] applying individual-patient data to quantify opioid utilisation (Table 1) have demonstrated a marked and persistent increase in opioid utilisation in the past three decades predominantly due to the increasing prevalence of opioid users and persistent use of opioids for patients with CNCP. Patients were more likely to receive opioids even though the annual number of clinical visits for CNCP and the underlying prevalence of CNCP did not increase when compared data in 2005 and 1980[2, 86]. In addition, persistent opioid utilisation rather than increasing opioid daily dose was the main reason for increasing opioid consumption[2, 85]. Persistent opioid users with a higher daily dose tended to use opioids more regularly than those with a

lower daily dose[84].

Similarly, in the UK, drug utilisation studies applied individual-patient data to quantify opioid utilisation found that the increasing prevalence of opioid users and persistent opioid utilisation in patients with CNCP were the main reasons attributing to increase opioid utilisation in the past two decades (Table 2) [29, 87-92]. A relative low opioid daily dose was found for patients without a cancer diagnosis when compared to those strong opioid users with a cancer diagnosis[29, 88]. However, there was an increasing trend of prescribing strong opioids in the general practices[90, 92] even the majority of CNCP patients received weak opioids as their index treatment[91].

Table 1. A summary of opioid utilisation studies applying individual patient data in the United States

Authors	Study design and data sources	Results	Conclusion
Caudill-Slosberg *et al.* (2004)[86]	A cross-sectional study using National Ambulatory Medical Care Survey in 1980 and 2000	The proportion of visits for musculoskeletal pain over all clinical visits did not change between 1980 (9.6%) and 2000 (9.9%). A higher proportion of visits for chronic pain were prescribed with opioids than other visits (8% and 16%). From 1980 to 2000, the proportion of prescribing with more potent opioids (e.g. morphine and oxycodone) increased from 2% to 9% of visits for musculoskeletal pain.	There was no increase in the number clinical visits for musculoskeletal pain, but opioids were more commonly prescribed at visits for musculoskeletal pain between 1980 and 2000.
Sullivan *et al.* (2008)[2]	A cohort study using data from the TROUP study from 2000 to 2005	The number of supply days and the cumulative annual dose of opioids increased by 30% to 50% from 2000 to 2005. The mean of supply dose and the underline prevalence of CNCP did not change.	Prolonged opioid use was the main reason of increasing opioid consumption.
Edlund *et al.* (2010)[85]	A cohort study using data from the TROUP study from 2000 to 2005	The top 10% of opioid users on the consumption ranking (by accumulated total dose) accounted for 82% of total opioid consumption in 2005 comparing to 77% in 2000.	Opioid users with high consumption were the main reason of increasing opioid consumption.
Von Korff *et al.* (2008)[84]	A cohort study using data from the CONSORT study from 1997 to 2005	Long-term opioid use episodes (more than 120 days of supply or more than 10 prescriptions filled) only accounted for 5.5% of all prescription episodes, but it accounted for 80% of all opioid consumption. Comparing the higher-dose long-term episode to the lower-dose long-term episodes, higher-dose episodes also had a higher prescription cover rate in the supply duration.	Long-term opioid utilisation was the reason of increasing opioid consumption . Higher opioid daily dose was tended to be associated with a higher prescription cover rate.

(Note) TROUP: Trends and Risks of Opioid Use for Pain, CONSORT: Consortium to Study Opioid Risks and Trends, CNCP: chronic non-cancer pain.

Table 2. A summary of opioid utilisation studies applying individual patient data in the United Kingdom

Authors	Study design and data sources	Results	Conclusion
Ashworth *et al*. (2013)[88]	A cross-sectional study using electronic prescribing records from low back pain patients participating in a prospective cohort study in the UK primary care	In the baseline period (30 days), 32.7% of patients with low back pain were prescribed with an opioid. The majority of opioid users (65%) were prescribed with opioids with mean daily OMEQ dose less than 20 mg/day, and there were only 10.7% of opioid users received opioids with the mean daily OMEQ dose higher than 50 mg/day.	The majority of opioid users received relatively lower mean daily dose of opioids.
Chevalier *et al*. (2014)[91]	A cohort study using CPRD from 2006 to 2011	Among all new opioid users for CNCP, about 90% were indexed on weak opioids, and 21.3% of all opioid users were chronic opioid users (continuously prescribing 183 days without a gap more than 30 days). The mean duration from opioid initiation to treatment discontinuation were 15 and 681 days for acute (less than 30 days) and chronic opioid users.	The majority of CNCP opioid users were indexed with weak opioids and used opioids for less than six months. However, parts of CNCP patients would become chronic opioid users with prolonged opioid prescribing.
Zin *et al.* (2014)[29]	A cross-sectional study using CPRD from 2000 to 2010	About 88% of strong opioid users were patients without diagnosis record of cancer. The annual days of supply increased from approximately100 days in 2000 to 150 days in 2010. The mean OMEQ dose per day did not change between 2000 and 2010 in patients without a cancer diagnosis. More than half (50.3%) of patients without a cancer diagnosis were prescribed opioids with mean daily dose less than 50 mg OMEQ dose per day.	Prolonged opioid use was a potential reason of increase strong opioid utilisation in the UK. However, strong opioids users without a cancer diagnosis in the UK might receive relatively lower mean daily dose than those strong opioid users with a cancer diagnosis.

Table 2. A summary of opioid utilisation studies applying individual patient data in the United Kingdom (continued)

Authors	Study design and data sources	Results	Conclusion
Bedson *et al.* (2013)[89]	A cross-sectional study using prescribing data from 12 GPs in Keele from 2001 to 2009	The annual prevalence of high dose weak opioid preparations increased from 507 to 955 per 10,000 registrants between 2001 and 2009. The annual prevalence of strong opioid preparations increased from 38 to 74 per 10,000 registrants between 2001 and 2009. After the launch of guidance which recommended using the lowest dose of NSAIDs and stopping Cox-2 inhibitors in patients with ischemic heart disease, there was a mark increased in level and trend of prevalence of opioid preparations.	Although the prescribing of opioid preparations increased from 2001, there was an increase in level and trend of opioid prescribing after the launch of guidance on NSAIDs prescribing.
Ruscitto *et al*. (2015)[92]	A cross-sectional study using individual patient data on dispensed analgesics in 1995 and 2010 in the Tayside region of Scotland	The proportion of residents who received opioids increased from 8.5% in 1995 to 11.0% in 2010. The majority of opioid users were prescribed with weak opioids in both 1995 and 2010. The proportion of residents who received strong opioids increased from 0.24% in 1995 to 3.6% in 2010.	Patients were more likely to be prescribed opioids, especially strong opioids from 1995.

Table 2. A summary of opioid utilisation studies applying individual patient data in the United Kingdom (continued)

Authors	Study design and data sources	Results	Conclusion
Bedson *et al.* (2016)[90]	A cross-sectional study using CPRD from 2002 to 2013	The annual incidence of long-term opioid prescribing episodes (more than 2 opioid prescriptions within 90 days) increased from 42.4 to 59.7 per 10,000 person-years between 2002 and 2011. Although the annual incidence of long-term opioid prescribing episodes increased, the proportion of long-term opioid prescribing episodes with a duration of more than one year remain stable. Within the first 90 days, the proportion of long-term opioid prescribing episodes which were prescribed with long-acting controlled opioids increased from 2.3% in 2002 to 10% in 2013.	The incidence of long-term opioid utilisation increased and there is a tendency that patients were more likely to receive opioids with higher potency from 2002.
Cartagena *et al.* (2017)[87]	A cross-sectional study using CPRD from 2000 to 2015	The proportion of CPRD registrants who received opioids increased from about 2.5% in 2000 to 5% in 2012. The proportion of individual opioid prescriptions which were more than 30 days increased from 15% in 2000 to 18% in 2013. The duration of continuous opioid prescribing periods (the time between two prescriptions is less or equal to 35 days) increased from 64 days in 2000 to 102 days in 2013. The mean daily number of tablets/capsules remained stable for individual prescriptions between 2000 and 2015.	Patients were more likely to be prescribed opioids in the UK from 2000. Prolong opioid prescribing rather than increased opioid daily dose was a potential reason of increase opioid utilisation in the UK.

(Note) CPRD: Clinical Practice Research Datalink, OMEQ: oral morphine equivalent, CNCP: chronic non-cancer pain, NSAIDs: Non-steroidal anti-inflammatory drugs, Cox-2: cyclooxygenase-2, UK: United Kingdom, GP: general practice

2.4. Controversies of persistent opioid utilisation for chronic non-cancer pain

Although the increased opioid consumption was found to be associated with the prolonged use of opioid for patients with CNCP, persistent opioid use for managing CNCP remains a controversial issue due to a lack of evidence-based knowledge about efficacy and safety of persistent opioid utilisation[3-5].

2.4.1. Efficacy and tolerability of opioid utilisation for chronic non-cancer pain

The analgesic efficacy of opioids has been examined in randomised controlled trials (RCTs) for various pain conditions. This section presents a synopsis of a rapid review on seven SRs published before October 2014 and synthesised the efficacy of opioids for patients with CNCP from RCTs which compared opioids with placebo or active controls[93-99]. SRs that included participants with cancer in the RCTs or admitted opioids by injection formulations were excluded from this rapid review. Most SRs (n=6) reporting evidence about opioid efficacy[94-99] used pain intensity or pain relief as the main outcome measure; only two SRs

reported function improvement[94, 98] (Table 3).

In general, a statistically significant but small improvement in pain intensity and physical function was found when opioids were compared to placebo. Nevertheless, no significant difference in pain relief was found when comparing opioids with other medicines, such as NSAIDs, tricyclic antidepressants (TCAs) or other antidepressants. In addition, NSAIDs were found significantly more effective than opioids in improving physical functional [94]. Once stratified on potency, strong opioids were slightly more effective in pain relief when compared to naproxen and nortriptyline[94, 97] (Table 4).

However, the synthesised results from RCTs need to be interpreted with caution due to the short follow-up period (generally less than three months) and heterogeneity in patient characteristics and outcome measures. All RCTs included in the seven SRs followed participants for less than three months, and hence the evidence of persistent opioid utilisation for CNCP from RCTs remains lacking. Unsurprisingly,

heterogeneity in patient characteristics and outcome measures was reported in several SRs due to the variety of pain conditions and tools to evaluate pain relief in RCTs.

Furthermore, the majority of RCTs excluded participants who are intolerant to opioid or participants with multiple medical conditions. For example, more than half of the RCTs included in the SR conducted by Chaparro *et al*. (2014) had a 'titration period' before randomisation to achieve an optimal dose for each patient[97]. Furthermore, most RCTs applied the per-protocol rather than the intention-to-treat principle to analyse the efficacy of opioid, which made their results in favour of opioid therapy because of selection bias (Table 3).

In addition, the high drop-out rate after randomisation and the relatively small number needed to harm (NNH) of discontinuation of opioid treatment implied poor tolerability due to adverse events or a lack of efficacy of opioid therapy for patients with CNCP. Based on five SRs, the NNH of experiencing any adverse event of opioid ranged from 5 to 14[93,

[94, 96-98]. The NNH of discontinuation of opioid treatment due to adverse events was 5 and 21 for patients with osteoarthritis[96, 98] and the NNH was 6 for patients with various types of CNCP[93].

Due to the short follow-up period and a poor tolerability in the RCTs, Krebs *et al.* (2018) conducted a pragmatic randomized trial in Veterans Affairs primary care clinics in the US to compare opioids with non-opioid medications over 12 months on pain-related function and pain intensity for patients with chronic back pain or hip or knee osteoarthritis. The results showed that there was no significant difference in the improvement of pain-related function between groups. Also, non-opioid medications were found to result in a better improvement in pain intensity when comparing to opioid users in the 12th month. This study implied opioids were not superior to non-opioid medications for functional improvement and pain intensity in the real-world practices over a one-year period[100].

Table 3. Characteristics of systematic reviews assessing efficacy of opioids for chronic non-cancer pain based on evidence from randomised controlled trials

Author	Pain condition	RCT duration	Sample size range	Drop-out rate range	Per-protocol analysis	Efficacy outcome measures
Duehmke *et al.* 2006[95]	Neuropathic pain	4, 6 weeks	21-131	I: 10-41% C: 15-41%	Yes	Pain intensity, pain relief
Chaparro *et al.* 2014[97]	Persistent low-back pain (≥12 weeks)	4, 15 weeks	56-1583	I: 28-59% C: 21-75%	Yes	Pain ratings, pain relief, sleep quality, non-opioid medication consumption
Costa *et al.* 2014[98]	Osteoarthritis	1, 4 weeks	53-2053	I: 0.6-2% C: 0-33%	Yes	Pain, function
Avouac *et al.* 2007[96]	Osteoarthritis	1, 4, 13 weeks	41-1011	I: 25% C: 7%	Yes	Pain intensity, physical function
Furlan *et al.* 2006[94]	CNCP	1, 13 weeks	8-846	I: 15-33% C: 30-38%	Yes	Pain intensity, pain relief, duration of morning stiffness, function, quality of life, mental state and mood, sleep quality
Moore *et al.* 2005[93]	CNCP	3 days, 8 weeks	40-755	I: 2-81% C: 5-65%	Not reported	Withdraw for lack of efficacy
Gaskell *et al.* 2014[99]	Chronic neuropathic pain or fibromyalgia	4, 6 weeks	45-159	I: 12-23% C: 10-32%	Yes	Pain intensity, psychological state, physical functioning, mental health, pain relief, rescue medication used

(Note) CNCP: chronic non-cancer pain; I: intervention arm; C: control arm

Table 4. Summary of main outcomes reported in systematic reviews assessing efficacy of opioids for chronic non-cancer pain based on evidence from randomised controlled trials

Author	Population	Comparison	Outcome measures	Results	Significantly favour
Placebo control					
Chaparro *et al.* 2014[97]	Low-back pain	Strong opioids vs. placebo	Pain intensity	MD: -0.43 (95%CI: -0.52, -0.33)	favour opioid*
			Proportion of patient achieved at least 30% of pain relief	NNT: 7	favour opioid*
			Proportion of patient achieved at least 50% of pain relief	NNT: 8	favour opioid*
Costa *et al.* 2014[98]	Osteoarthritis	opioids vs. placebo	Pain relief	NNT: 10	favour opioid*
			Functional improvement:	NNT: 12	favour opioid*
Avouac *et al.* 2007[96]	Osteoarthritis	opioids vs. placebo	Pain intensity	MD: -0.79 (95%CI: -0.98, -0.59)	favour opioid*
Furlan *et al.* 2006[94]	CNCP	opioids vs. placebo	Pain relief	MD: -0.6 (95%CI: -0.69, -0.5)	favour opioid*
			Functional improvement	MD: -0.31(95%CI: -0.41, -0.22)	favour opioid*
Active control					
Furlan *et al.* 2006[94]	CNCP	When comparing strong opioid to naproxen or nortriptyline	Pain relief	MD: -0.34 (95%CI: -0.67, -0.01)	favour opioid*
		When comparing strong opioid to NSAIDs and TCAs	Pain relief	MD: -0.05 (95%CI: -0.32, 0.21),	non-significant difference
		When comparing strong opioids to NSAIDs	Functional improvement	MD: 0.19 (95%CI: 0.05-0.33)	favour NSAID*

(Note) * p<0.05, MD: mean difference, NNT: number needed to treat, NSAID: non-steroidal anti-inflammatory drug, TCA: tricyclic antidepressants

2.4.2. Risk of higher opioids-related adverse effects in persistent opioid users

Persistent opioid exposure was found to be associated with increased risks of adverse effects, emergency department visits and mortality in real-world data[6-9]. Opioid-related adverse effects (such as respiratory depression, euphoria, sedation and dependence) are dose-dependent[48], and hence a higher dose and poor opioid metabolism increase the risk of adverse events. Persistent opioid users have been found increasing opioid dose[40, 101, 102], combining opioids and CNS sedatives[9, 103-105] and having a higher risk of problematic opioid use[106, 107].

Persistent opioid exposure may lead to in an increased opioid dose due to the opioid tolerance[6]. WHO defines 'tolerance' as the reduction in response to a drug after continued use, and it can be attributed by both pharmacokinetic and pharmacodynamic mechanisms[108]; consequently, a higher dose is required to achieve the original response once patients have developed tolerance of a drug[109]. This is commonly found in patients with CNCP who receive opioids for a long term. Several published studies which applied different methods to define persistent

opioid utilisation in patients with CNCP across different countries have found a higher opioid daily dose among the persistent opioid users compared with non-persistent opioid users [40, 101, 102] (Table 5).

In addition, persistent opioid utilisation was associated with a higher risk of addiction, abuse and problematic opioid use[6]. Literature has suggested that the risk of 'problematic opioid use' was greater among patients prescribed opioids for pain when compared to the general population[110-112], but the risk of 'problematic opioid use' among persistent opioid users is controversial due to differing definitions of 'problematic opioid use'.

Table 5. Summary of cohort studies applying individual-patient data to measure an increased opioid daily dose of persistent opioid users

Authors	Study design and countries	Patients	Definition of persistent opioid users	Results
Fredheim *et al.* (2013)[102]	A cohort study following patients for 5 years in Norway	New strong opioid users without cancer diagnosis	Patients received their second opioid prescription within 70 days after opioid initiation	The mean daily dose increased more than 25% in the fifth year for 58% of the chronic opioid users when compared to the mean daily dose in the first year. For about 33% of the chronic opioid users, their mean daily dose doubled in the fifth year.
Henry *et al.* (2015)[101]	A cohort study following patients for 1 years in California	New opioid users with musculoskeletal pain	Patients receiving at least one opioid prescription in each of 4 calendar quarters	About 9% of persistent opioid users increased the opioid daily dose more than 30 mg OMEQ dose in the final quarter when compared to opioid daily dose in the first quarter.
Mellbye *et al.* (2015)[40]	A cohort study following patients for 6 years in Norway	New persistent opioid users without cancer diagnosis	Multiple-dimension algorithm measured opioid persistence in each patient-year*	For patients who were new persistent opioid users in the first patient year and remained in persistent utilisation for 6 years, more than 65% of them increased their annual opioid dose by more than 25% and 22% of them increased their annual opioid dose by 200%.

(Note) *The multiple-dimension algorithm is a composite of three dimensions including annual dose (≥4500 oral morphine equivalent dose), annual number of prescription and annual number of quarters covered with prescription (≥3) during the same patient-year. OMEQ: oral morphine equivalent

The estimated risk of opioid addiction associated with persistent opioid utilisation was relatively lower in the studies published in the 1970s and the early 1980s[113-115] due to uncritical methodology and selective interpretation. For example, opioid abusers were defined as patients with dose exceeded by at least 50% of the maximal recommended dose rather than psychological or physical dependence in the study conducted by Medina *et al*. (1977)[114]. From the early 2000s, a series of reviews raised the concerns on the variation in the definitions of problematic opioid use in published studies and the under-reporting of problematic opioid use in clinical trials that led to biased estimates of risk associated with problematic opioid use [116-119].

In response to the issues of measuring and reporting problematic opioid use in clinical trials, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) summarised the challenges in assessing abuse liability and provided a list of definitions for problematic opioid use to improve the record of abuse liability in 2013[120]. In addition, the Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION) suggested a framework to measure abuse

liability for the use of opioids for chronic pain in clinical trials[121] (Table 6).

Table 6. Summary of definition of misuse, dependence and problematic opioid use from the consensus statements of IMMPACT and ACTTION panels

Term	Definition
Misuse	The use of medications for a medical purpose does not follow medical indications or prescribed dosing, regardless of the presence or absence of harm[122].
Dependence	A physiological response that is manifested by a drug class specific withdrawal syndrome due to a rapid reduction in exposure, such as abrupt cessation and rapid dose reduction or exposure to an antagonist[123].
Abuse	Any use of an illegal drug or the intentional use of a medication for a nonmedical purpose, such as getting high[120, 121].
Addiction	A primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by medication-taking behaviours with experience of, or demonstrated potential for harm including impaired control over drug use, compulsive use, continued use despite harm and craving[123]
Aberrant opioid-related behaviours or problematic opioid use	Any behaviour that suggest the presence of opioid abuse or addiction. Chabal *et al.* (1997) provide a comprehensive list of five essential criteria to identify problematic opioid users for patients treated with opioid for pain[120, 121, 124].

Boscarino *et al.* (2011) conducted interviews on more than 705 patients who were persistent opioid users (i.e. receiving 4 or more opioid prescriptions in the last 12 months) and randomly selected from nine

primary care clinics and three specialty care clinics in Pennsylvania, and found 35% of them met the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for an opioid use disorder[125]. In 2013, Boscarino *et al.* re-analysed their data by applying the final DSM-5 criteria after the consensus statements from the IMMPACT and ACTTION panel, and found the prevalence of opioid use disorder for persistent opioid users is 41.3%[106].

In addition to the increased risk of opioid tolerance and dependency and hence higher opioid dose and risk of opioid use disorder, common psychological illnesses were found among persistent opioid users[6, 40]. Medications for depression, anxiety and insomnia are often prescribed to patients to control common symptom related to chronic pain[10-12], but the interaction between opioids and CNS depressants increased the risk of oversedation[13, 14]. Published literature has shown a higher proportion of persistent opioid users were prescribed with CNS depressants concurrently even the definitions of a persistent opioid user and concurrent use were varied between studies[43, 103, 105] (Table 7).

Table 7. Summary of studies applying individual patient data to measure concomitant sedatives between persistent and non-persistent opioid users

Authors	Study design and countries	Patients	Definition of persistent opioid users	Definition of concurrent sedatives	Results
Sun *et al.* (2017)[43]	Retrospective cohort study in the US 2001 to 2013	Non-cancer pain patients who filled at least one opioid prescription between 2001 and 2013	Patients received more than 10 opioid prescriptions or 120-day supply in a given year	One day overlap of opioids and benzodiazepines prescription based on prescribing records	Higher proportion of persistent opioid users was prescribed with benzodiazepines concurrently in every year from 2001 to 2013 when compared to other opioid users.
Huang *et al.* (2016)[105]	Cross-sectional study in the US 2002 to 2014	Opioid users between 2002 and 2014	Patients received opioid prescriptions at least 90 days between 2002 and 2014 and there was no gap more than 7 days between prescriptions within the 90 days.	Patients with a benzodiazepine episode that overlapped an opioid episode by at least 7 consecutive days.	Higher proportion of persistent opioid users concomitantly used benzodiazepines in any given year from 2002 to 2014 when compared to other opioid users.
Mellbye *et al.* (2012)[103]	Cross-sectional study in Norway 2008	Non-cancer pain patients who filled at least one opioid prescription in 2008	Multiple-dimension algorithm*	Any benzodiazepine or z-hypnotics prescription in 2008.	Higher proportion of persistent opioid users combined and was prescribed with greater annual dose of benzodiazepines or z-hypnotics with opioid when compared to other opioid users.

(Note) *Multiple-dimension algorithm is a composite of three dimensions including annual dose (≥4500 oral morphine equivalent dose), annual number of prescription and annual number of quarters covered with prescription (≥3) during the same patient-year. US: United States

2.5. Incidence and determinants of opioid-overdose deaths in the US

In the past decade, there has been a marked increase in opioid-related mortality in several western countries that coincided with increasing opioid utilisation[15, 16, 126]. Several studies have estimated the incidence of opioid-overdose deaths among the general population, and the increase in prescription opioids has been closely associated with the rise in opioid-overdose death from 2000[15-18].

In the US, the increase in drug-overdose deaths from 1990 has been associated with the rise in opioid overdose[15, 16, 18]; up to 2014, more than 60% of drug-overdose deaths involved an overdose of opioids[18]. According to the US Centers for Disease Control and Prevention (CDC), from 2000 to 2015, the annual incidence of overdose deaths involving opioids in the US increased from 3 to 10 deaths per 100,000 population[127]. As the opioid-overdose death is linked to a two-year drop in life-expectancy in the US, it was declared as a national public health emergency by the US President in 2017[20]. Reducing opioid-overdose death is a priority of public health policy in the US, and was retained as

one of the Healthy People 2020 objectives[21].

2.5.1. Correlation between prescribing opioids and opioid-overdose deaths

According to the US CDC, opioid-overdose death is defined as death that happens when opioid is taken in excessive amounts and caused injury to the body (poisoning)[22]; namely, the transient increase in opioid dose is the cause of opioid-overdose death[21]. According to the CDC's statistics on the annual number of opioid-overdose deaths between 2000 and 2015[127], prescribing opioids have become the main reason of opioid overdose deaths in the US rather than illicit drugs, such as heroin[127].

Between 2000 to 2014, the most frequently reported opioids involving in opioid-overdose deaths were nature and semisynthetic opioids (oxycodone followed by hydrocodone)[128, 129], and the incidence has steadily increased from 2000. Of the four categories of CDC's statistics of opioid-overdose deaths, i.e. heroin, nature and semisynthetic opioids

(e.g. oxycodone and hydrocodone), other synthetic opioids (e.g. fentanyl and tramadol) and methadone, although the trend of deaths involving heroin escalated from 2010 and marginally exceeded nature and semisynthetic opioids in 2015, the incidence of deaths involving synthetic opioids other than methadone sharply increased three times from 2013 to 2015[127, 130].

2.5.2. Other risk factors associated with opioid-overdose deaths

King *et al.* (2014) conducted a SR of observational studies which reported quantitative evidence about the determinants of opioid-overdose death between 1990 and 2013[45]. Seventeen determinants were identified from 47 studies (including cohort, case-control and cross-sectional studies) conducted in the US and Canada. The majority of opioid-related adverse events, such as respiratory depression were dose-related, and hence most epidemiology studies in North America explored the association between high opioid prescribing and opioid-overdose deaths, and King *et al.* (2014) grouped those determinants into three categories, including patients' characteristics, prescribing behaviour and systemic determinants, such

as the implementation of the Prescription Drug Monitoring Program (PDMP)[45].

Patient characteristics associated with opioid-overdose deaths included opioid diversion, doctor shopping, drug substitution, multiple substance toxicity, history of substance abuse and sociodemographic characteristics. Of the sociodemographic characteristics, male, middle age, non-Hispanic Whites and American Indian/Alaska Natives and lower socioeconomic status (SES) were associated with higher risk of opioid-overdose deaths[45].

Prescribing behaviour, such as prescribing a selected opioid preparation (e.g. strong opioids, oxycodone), high-volume prescribing and high opioid dosage were associated with opioid-overdose deaths[45]. Prescribing of long-acting oral formulations of strong opioids was associated with opioid-overdose deaths in the US and Canada due to a relatively high dose obtained in pills.

Gomes *et al.* (2011) used a claim-based database, the Ontario Public

Drug Programs between 2003 and 2008 to measure the prescription rate of opioids (i.e. the number of patients who received individual opioids per 1000 patients per year) in Ontarians aged between 15 and 65 years old, and found the number of patients who received long-acting oxycodone doubled in 6 years in contrast to decreasing or remained prescription rate of other opioids. Coincidently, opioid-overdose mortality increased during the same period[131]. This indicates that prescribers may not be aware of the dose varied by formulations of opioids and over-prescribe strong potency and high dose of opioid preparations would lead to opioid-overdose deaths.

Many epidemiological studies have explored the association between daily dose of prescribing opioids and opioid-overdose deaths in the North America[7, 9, 41, 42]. Under the notion that opioid-related analgesic effects and adverse effects are dose-depenent[48], the majority of North American based studies measured opioid daily dose in a short period of time ranged from 1 to 90 days before the date of opioid-overdose death to evaluated its association with opioid-overdose death. Based on those published literature[7, 9, 41, 42], opioid daily dose (OMEQ dose 100 to 200

mg/day) was found associated with increased risk (odds ratio (OR) ranged from 2.04 to 8.9 when comparing to patients received opioid less than OMEQ dose 20 mg/day) of opioid-overdose deaths in the US and Canada. In addition, multiple substance toxicity was commonly found among opioid-overdose deaths, and BZDs and antidepressants were the most common medicines to be mentioned (Table 8).

Following a study identifying the association between opioid mortality and opioid daily dose[132], the US CDC updated opioid prescribing guidance in 2016, and the OMEQ dose of less than 50 mg/day was recommended for patients with CNCP to avoid opioid-related harm, and the combination of opioids and BZDs was not recommended[19]. However, it has been argued that the CDC guideline is based on limited evidence as the majority of studies were observational studies with notable limitations, such as incomplete or no adjustment of confounding factors and measurement error on opioid prescriptions or opioid-overdose deaths[19]. A brief review conducted by Ranapurwala *et al.* (2018) examined the studies cited in the CDC guidance and recommended further studies should apply big data sources and link multiple data

sources to identify potential confounding factors and examine measurement error by sensitivity analysis[133].

Table 8. Summary of studies applying individual-patient data to identify the association between opioid-overdose death and daily opioid dose in North America

Authors	Study design	Patients	Outcome	Definition of opioid overdose death	Opioid daily dose measure interval	Results
Dunn *et al.* (2010)[9]	Cohort study	Adults patients receiving 3 or more opioid prescriptions in 90 days and did not have cancer diagnosis	Opioid overdose	An ICD code indicating opioid-related poisoning or an ICD code indicating an adverse opioid-related event with a combination of an ICD code indicating an overdose	90 days before opioid-overdose	Patients received the mean daily OMEQ dose of 100 mg/day had an 8.9-fold increase in the risk of overdose when comparing to those receiving mean daily OMEQ dose of 0 to 20 mg/day. An increased risk for opioid users who received any sedative within 3 months before the events was found.
Gomes *et al.* (2011)[42]	Nested case-control study	Patients without cancer diagnosis and received at least one oral form opioid prescription	Opioid-over dose deaths	Deaths from the Office of the Chief Coroner of Ontario database in which the coroner determined that a combination of drugs (including opioid) resulted in death, or those in which forensic toxicologic testing revealed opioid concentrations sufficiently high to cause deaths.	On the event date	Patients received mean daily OMEQ dose of 200 mg or more had a nearly 3-fold increase in the risk of opioid-overdose deaths against those received less than 20 mg OMEQ dose.

(Note) CNCP: chronic non-cancer pain, ICD: International Classification of Disease code, OMEQ: oral morphine equivalent

Table 8. Summary of studies applying individual patient data to identify the association between opioid-overdose death and daily opioid dose in North America (continued)

Authors	Study design	Patients	Outcome	Definition of opioid overdose death	Opioid daily dose measure interval	Results
Bohnert *et al.* (2011)[7]	Case-cohort study	A 5% random sample of those patients received any opioid in 2004 and 2005	Opioid-overdose deaths	ICD code indicating deaths due to any medication with a combination of a ICD code indicating opioids poison	On the event date	The hazard ratio of opioid-overdose deaths was 7.2 among patients with CNCP received the mean daily OMEQ dose of 100 mg/day or more against those received less than OMEQ dose 20 mg/day .
Dasgupta *et al.* (2016)[41]	Cohort study	Opioid users in 2005	Overdose deaths involving opioids	The outcome was defined as any overdose where at least one opioid substances were deemed by the medical examiner to be involved.	During 2005	An association between higher mean daily OMEQ dose and opioid overdose mortality was found. Patients ever received benzodiazepine during one-year follow-up period were at a ten times higher risk.

(Note) CNCP: chronic non-cancer pain, ICD: International Classification of Disease code, OMEQ: oral morphine equivalent

2.6. Opioid-related deaths in the UK

In the UK, there is also an increasing trend of opioid-related mortality. However, the incidence and determinants are less well described compared to North American countries. The monitoring of opioid-related mortality initiated from the concerns of drug-misuse deaths as there has been an increasing trend of drug-misuse deaths in England and Wales paralleled with the rising death involved heroin/morphine from 1990[28].

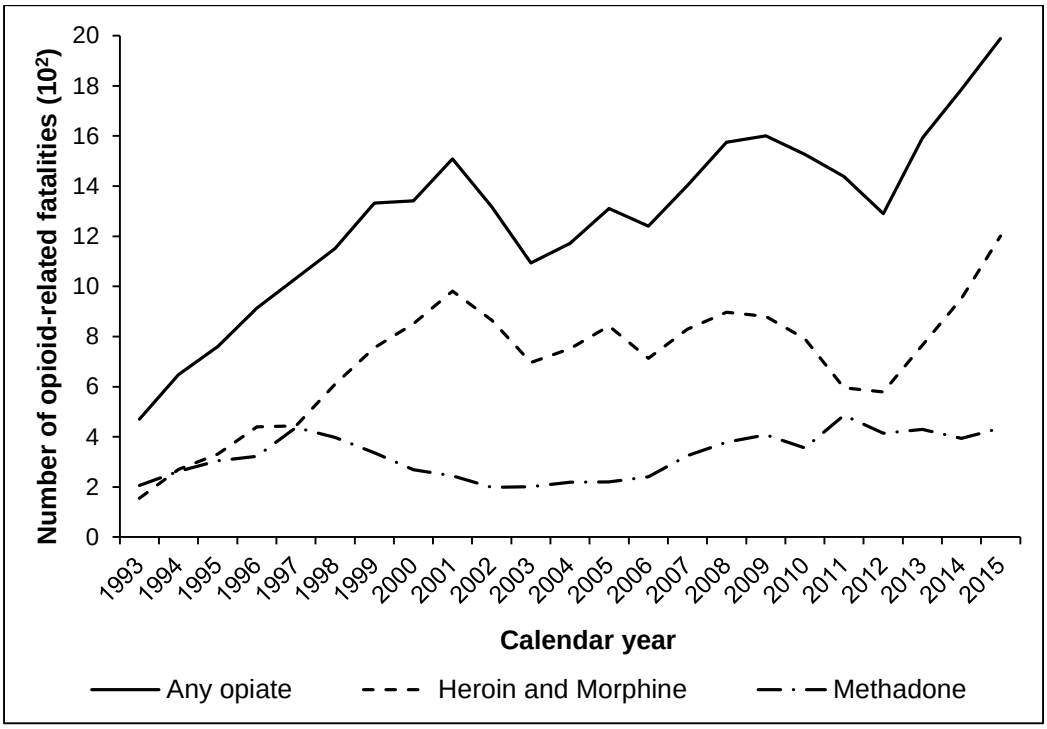
2.6.1. Correlation between heroin, methadone and opioid-related death in the UK

The number of drug misuse deaths increased from 1990 in the UK, which was driven by an increasing number of people using heroin from 1980[25]. The European Drug Report 2017 identified 8,441 drug misuse deaths occurred in Europe in 2015, and the UK accounted for 2,655 (31%) of drug misuse deaths; of which, 1200 (45.2%) involved heroin[134]. Due to the concerns on the misuse deaths related to heroin, the UK ONS routinely monitors the number of 'drug misuse death' which is defined as deaths where the underlying cause is drug abuse, dependence and poisoning[23, 24].

‘Opioid-related death’ is a subset of drug misuse deaths when an opioid was mentioned on the death certificate[23, 24]. As the definition of ‘opioid-related death’ originates from drug-misuse death which included deaths related to drug abuse, and hence the annual trend of opioid-related death is highly correlated with substance abuse and abstinence. From 1990, the trend of increasing opioid-related deaths in England and Wales paralleled with the increasing deaths involved heroin/morphine[28], and it reached the peak in 2001 (1509 deaths)[28, 135]. Between 2002 and 2010, the number of opioid-related deaths varied due to the cessation of opium cultivation in Afghanistan in 2000 and subsequent increases in the purity of heroin at street level[25, 28, 136]. During 2010 and 2012, the number of opioid-related deaths slightly decreased that might be attributed by the ‘heroin drought’ (i.e. the reduced availability and purity of heroin at street level) due to crop failures in the Afghan poppy fields and conflict in Pakistan and Afghanistan[26, 27], but rose 54.2% between 2012 and 2015 due to subsequently increased availability of heroin. Finally, the incidence of opioid-related deaths among the general population was 6.5 fatalities /100,000 population in England and Wales in 2015[25, 28] (Figure 4).

In contrast with heroin/morphine-related deaths, methadone-related deaths were mainly associated with the adoption of opioid substitution treatment and the substitution effect to heroin. Despite the number of methadone-related deaths decreased from 1997 (437 deaths) due to the introduction of daily dispensing and supervision of methadone dosing to reduce diversion[28, 135], the number of methadone-related deaths gradually increased in England and Wales from 2004 due to the promotion of getting patients to complete opioid substitution treatment in England since 2000[137]. Leaving treatment and many transitions into and out of treatment were associated with the frequent relapse of dependence and a higher risk of overdose and deaths[137-139]. During the 'heroin drought' period (2010 to 2012), the number of methadone-related deaths increased 37% as methadone potentially to substitute heroin[25] (Figure 4).

Figure 4. Annual number of opioid-related death involving heroin/morphine and methadone in England and Wales



(Note) This figure was generated from the published statistics from the ONS[28]

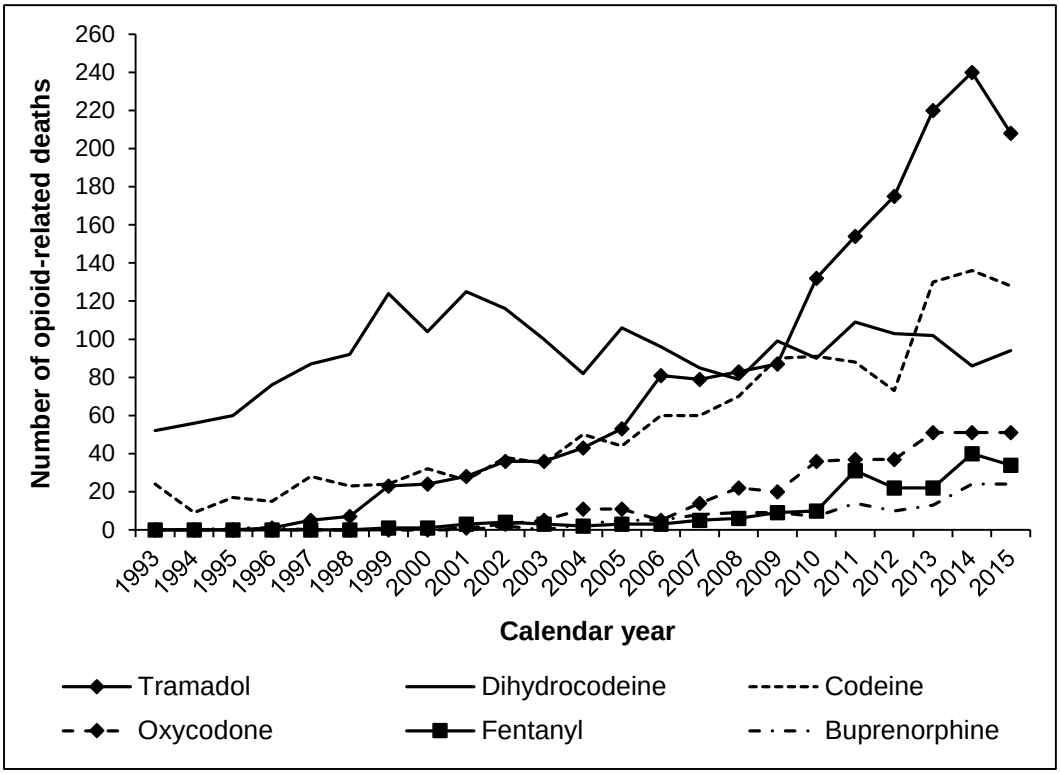
2.6.2. Correlation between prescribing opioids and opioid-related death in the UK

The statistics published by the ONS combined deaths where heroin or morphine was mentioned on the death certificate[28] because heroin is metabolised into morphine in the human body and the current post-mortem test in England and Wales cannot identify deaths which occurred as a result of the use of heroin or morphine. Although the

change in the number of opioid-relate deaths in England and Wales was mainly related to heroin/morphine-related deaths which were influenced by the availability and purity of heroin in street level, the number of deaths related to prescribing opioids (except methadone) paralleled with the increase in opioid prescribing related to persistent use for CNCP in England and Wales from early 1990s[25, 28, 29].

Stratifying the annual trend of opioid-related deaths by the type of prescribed opioids that involving the opioid-related deaths, dihydrocodeine was the most commonly prescribed opioid involved in opioid-related deaths before 2009. Nevertheless, the number of tramadol-related deaths gradually increased since 1998 with the increase in tramadol prescribing, and subsequently tramadol became the most commonly reported prescribed opioid for opioid-related deaths from 2010 in England and Wales, and 1715 people died with tramadol up to 2015 since the first case recorded in ONS death certificate in 1996[28] (Figure 5).

Figure 5. The annual number of opioid-related deaths involving prescribed opioids in England and Wales



(Note) This figure was generated from the published statistics from the ONS[28]

In addition, the number of codeine-related deaths also increased with increasing codeine prescribing[38]. There was also an increasing trend in both oxycodone- (14 vs 51) and fentanyl- (5 vs 24) related deaths between 2007 to 2015[28] (Figure 5). Although the number of opioid-related deaths involving strong opioids (e.g. oxycodone and fentanyl) also increased in England and Wales, in contrast to the US

where strong opioids have been associated with substantial increases in opioid-overdose deaths[129], the most common prescribed opioids involving in opioid-related deaths in England and Wales were weak opioids (e.g. tramadol and codeine).

2.6.3. Risk factors associated with opioid-related deaths in the UK

Compared to opioid overdose deaths in the US which were mainly induced by excessive amounts of opioids, opioid-related deaths in the UK involved a complex mechanism related to the use of an illicit drug, inadequate chronic pain management and persistent opioid utilisation[22-24].

To reduce drug-misuse deaths especially opioid-related deaths, the Advisory Council on the Misuse of Drugs (ACMD) reviewed evidence from official statistics and published studies about opioid-related deaths in the UK and identified factors associated with increasing opioid-related deaths[25]. In addition to the availability of heroin[26, 27, 136] and the

implementation of opioid substitution treatment[135, 138, 139], determinants associated with the ageing cohort of people who using heroin since 1980, deprive SES, and persistent utilisation of prescribing opioids for chronic pain were identified.

Stratifying the ONS aggregate-level statistics of opioid-related deaths by different age groups, the group with the highest age-specific mortality rates of opioid-related deaths changed over time. In 2001, people aged between 20 and 29 years had the highest age-specific mortality rates of opioid-related deaths (91.1 per million inhabitants) when compared to people at other age groups[28]. However, between 2003 and 2013, people aged between 30 and 39 years had the highest age-specific mortality rates of opioid-related deaths. From 2014, people aged between 40 and 49 years subsequently had the highest age-specific mortality rates of opioid-related deaths (88.4 per million inhabitants)[28].

In addition to an increasing trend of prescribing long-acting opioids to elderly patients in the UK[90], this trend can also be explained by the

epidemic heroin abuse in the 1980s. As the patients who used heroin since 1980 aged, the ACMD assumed that multiple comorbidities, such as respiratory diseases, cardiovascular diseases and psychological illness would potentially make patients more vulnerable and a higher risk of opioid-related deaths among heroin users was identified when they become older[140].

Poverty, unemployment and homelessness have been linked to problematic drug use[141-143]. In the 1980s and early 1990s, poverty in de-industrialised areas in the UK was identified as the cause to use heroin[144]. Since 1993, the difference in life expectancy between residents with the highest and the lowest SES gradually increased in England and Wales[145], and hence SES has been recognised as an essential determinant of public health. Applying practice-level dispensing data in England to quantify opioid prescribing found that the higher deprivation measured by the Index of Multiple Deprivation was associated with increasing opioid prescribing[146]. In addition, from 2000, the lower super output areas (geographic hierarchy areas for reporting small statistics) with higher deprivation were found to have a higher

age-standardised mortality rate of drug-related deaths[25].

In addition to increasing age and SES, the increasing number of opioid-related deaths in England and Wales paralleled with the increase in opioid prescribing related to persistent opioid utilisation for CNCP[25, 28, 29]. However, as the definition of opioid-related death is originated from drug-misuse death, it is not possible to directly infer the causality between persistent opioid utilisation and opioid-related deaths. In fact, the proportion of opioid-related deaths involving only one opioid over all opioid-related deaths decreased from 76% to 53% between 2000 and 2014 in England and Wales[147]. In 2013, approximately 70% of heroin/morphine-related deaths and 70% of tramadol-related deaths were recorded as involving other substance, and alcohol was the most common substance be mentioned followed by antidepressants, other opioids and BZDs[25].

In contrast to epidemiological evidence from North American countries, currently, the incidence and determinants of opioid-related deaths and

its association with opioid dose, persistent opioid use and concomitant medicines in the UK are still unclear. Consequently, the current prescribing recommendations in the UK, such as an OMEQ dose less than 120 mg/day is the recommended maximum dose to prevent serious opioid-related adverse events[5], are not evidence-based.

In the US, the evidence has shown that the influence of factors on opioid overdose death changed across geographic regions due to the variation in population characteristics, prescribing behaviour and systemic determinants. For example, the proportions of opioid-overdose deaths involving doctor shopping was 21% in West Virginia[148], but only 2% of opioid-overdose deaths showed evidence of doctor shopping in Ontario[149]; and hence the association between opioid-overdose deaths and opioid diversion were different among West Virginia[148], Vermont[150], western Virginia[151], Ontario[149] and Utah in the US [152]. As there is a notable variation in epidemiology, utilisation of prescribing opioids and outcome measures (e.g. opioid-related deaths in the UK and opioid overdose deaths in the US), the evidence from North Americans countries cannot be directly applied to the practice in the UK.

2.7. Safety issues of tramadol utilisation

Although the evidence about the association between opioid-related death and utilisation of prescribing opioids in the UK is generally lacking, regulation decisions need to be made for managing critical safety-related issues. Tramadol, the most commonly prescribed opioid involving in opioid-related death in the UK, was classified as a Schedule III controlled drug from June 2014 to control increasing tramadol utilisation and tramadol-related deaths[33]. The clinical and regulatory approaches for balancing risk and benefit of tramadol intrigued the motivation of this PhD study. Therefore, tramadol classification was used as a case study to develop this PhD research framework.

Tramadol is a synthetic analogue of codeine, and it is indicated for moderate to severe pain in the UK. In addition to working as an opioid mu-receptor agonist, tramadol inhibits the reuptake of serotonin and norepinephrine and hence inhibit the pathway of pain transmission in the CNS[153]. Due to its dual pharmacological mechanism that acts on the opioid receptors and inhibits the reuptake of serotonin and norepinephrine at the same time[31], traditionally, tramadol has been

considered relatively safe with a lower risk of addition compared to other strong opioids[32]. Furthermore, due to the inhibition of serotonin and norepinephrine reuptake which provide an antidepressant-like effect, tramadol has been prone to be prescribed for patients with co-existing depression[154].

2.7.1. Increasing tramadol utilisation and efficacy of tramadol for manging chronic non-cancer pain

An increasing trend of tramadol utilisation has been found in several western countries. Studies in the US and Germany found that tramadol was prescribed more frequently, and a small proportion of tramadol users became persistent users and consumed a considerable amount of tramadol, and thus suggested that the prolonged use of tramadol and high quantity of prescribing tramadol lead to the increase in tramadol consumption[84, 155].

In Germany, Tholen *et al*. (2012) conducted a cross-sectional study in 2007 using claims data and found that only 7.9% of tramadol users

(received at least one tramadol prescription) were categorised as high-volume tramadol users (i.e. patients prescribed tramadol with an annual dose higher than 180 DDDs) but 57% of the overall annual tramadol utilisation in 2007 was prescribed for those high volume tramadol users. Moreover, 33.2% of overall annual tramadol use was prescribed to 2.8% of tramadol users who received tramadol more than 360 DDDs in 2007[155].

Similar to the increasing utilisation trend of other opioids in the UK, data from the NHS BSA showed that the number of DDDs of tramadol doubled from 2005 to 2012[33]. However, the reasons underpinning the increased use of tramadol are unclear.

Gore *et al*. (2011) conducted a cohort study by applying The Health Improvement Network (THIN) database in the UK to follow the utilisation of tramadol for patients with osteoarthritis and chronic low back pain. 'Discontinuation' was defined as a gap more than 60 days between the end of the previous prescription and the start of the next prescription.

The result showed that 65% of tramadol users with osteoarthritis and 69.3% of tramadol users with chronic low back pain discontinued tramadol treatment in the second month and about 90% of all tramadol users discounted tramadol treatment in one year[156, 157]. However, Gore *et al.* only followed patients to the first discontinuation, and it is possible that patients would re-initiate tramadol treatment as chronic pain is often intermittent and recurrent[156, 157].

Cartagena *et al.* (2017) conducted a cross-sectional study using CPRD and found the average length of individual prescriptions, the length of continuous prescribing periods and the proportion of individual prescriptions more than 30 days in each calendar year between 2000 and 2015 gradually increased and suggested prolong prescribing caused the increase in opioid utilisation in the UK[87]. However, Cartagena *et al.* analysed opioids as a class rather than explored the reasons of increasing use of individual opioids[87]. Currently, there is no study applying longitudinal individual-patient data to explore the reasons of increasing utilisation for individual opioids in the UK.

Although it is still unclear whether prolonged utilisation is the main reason of increasing tramadol utilisation, similar to the efficacy evidence of opioids overall, the efficacy of tramadol for CNCP was assessed for less than 3 months in RCTs and the discontinuation related to poor tolerability or a lack of efficacy was common [94, 95, 158]. In addition, the majority of RCTs excluded patients with complicated or serious medical conditions, such as impaired renal or hepatic function[95, 158]. Nausea was the most frequent adverse effects when patients used tramadol for CNCP in RCTs. Chaparro *et al.* (2013) found the NNH of tramadol-related nausea, somnolence and constipation were 11, 16 and 17 respectively compared to placebo in low back pain patients[158]. In addition, Hollingshead *et al.* (2006) summarised evidence about the tolerability of tramadol from RCTs and reported the NNH for tramadol withdrawal due to adverse events was 7[95].

2.7.2. Tramadol related serious adverse events

An increasing trend of tramadol-related deaths has been found in the UK from 1996. In England and Wales, the number of opioid-related deaths involving tramadol increased gradually, and it rose four-fold from 2004 to

2014[28]. In Northern Ireland, tramadol-related deaths represented 9% of drug-related deaths in 2001 and rose to 40% in 2011 [37]. In England and Wales, the proportion of opioid-related deaths involving tramadol (10.5%) was higher than codeine (6.4%) in 2015, despite more prescriptions for codeine being dispensed in the same year[28].

There are limited epidemiological studies that explore determinants of tramadol-related death. As tramadol has been considered relatively safe and less potency compared with other strong opioids[32], only one of the previous nested case-control studies[9] that assessed the association between opioid-overdose death and opioid daily dose in North America included tramadol[7, 9, 42, 132]. A case review conducted in Northern Ireland using the registration of post-mortem toxicological analysis from 1996 to 2012 suggested that more than half of tramadol-related deaths were persistent tramadol users as most of them were diagnosed with chronic pain and prescribed tramadol in combination with CNS depressants, such as opioids, BZDs and anti-depressants[37].

There are other rare and serious adverse effects associated with tramadol. Tramadol has been found to reduce the seizure threshold, and cases of seizure have been reported in patients treated with both therapeutic and high dose tramadol[159]. In addition, the combination of tramadol and serotonergic antidepressants increases the amount of serotonin[159]. Furthermore, the combination of tramadol and cytochrome P450 isoenzyme 2D6 (CYP2D6) inhibitors (e.g. paroxetine, fluoxetine and duloxetine) reduced the clearance of tramadol and increased the amount of serotonin. Those interactions are prone to induce serious adverse events (e.g. serotonin syndrome) due to the inhibition of serotonin reuptake, the release of serotonin and decreased metabolism of tramadol[160-163]. The inhibition of serotonin reuptake may also cause potentially fatal hypoglycaemia for tramadol users[164] as it induces increasing utilisation of peripheral glucose via the glutamate receptor 4. Opioids (including tramadol) and serotonin may increase the release of anti-diuretic hormone and result in impaired water excretion and hyponatremia[165].

Currently, the association between serious adverse events and

long-term tramadol utilisation is unclear due to a lack of epidemiological studies. Although the potential interaction between tramadol and serotonergic antidepressants might cause serious adverse events, in the UK, the association between serious adverse events and short-term tramadol utilisation was studied within 90 days after tramadol initiation (Table 9)[166-169]. A case review of tramadol-induced seizures suggested that seizure could happen up to one year after tramadol initiation[170] as increasing dose was often found among long-term opioid users[40, 101, 102]. For persistent opioid users, increasing annual opioid dose was associated with a higher chance of concomitant use of antidepressants[104], and hence persistent tramadol users might also receive higher prescriptions of tramadol and antidepressants and have a higher risk of serious adverse events.

2.7.3. Limit accessibility of opioid analgesics

To manage increasing harms and opioid utilisation via the prescribing route, limiting accessibility, such as re-classifying opioid schedule or withdraw of product from the market are commonly used strategies.

For example, co-proxamol (the combination of dextropropoxyphene and paracetamol) was the most common single medicine implicated in suicide in England and Wales[171-176] between 1997 and 1999. Therefore, the Committee on Safety of Medicines suggested to withdrew co-proxamol from the UK market in January 2005 due to safety concerns[177]. In the US, Food and Drug Administration (FDA) removed propoxyphene (dextropropoxyphene is a dextro-isomer of propoxyphene) from the market on 19 November 2010 due to the accumulating data regarding cardiotoxicity[178]. To control misuse and abuse involved hydrocodone/acetaminophen combination[179, 180], the US Drug Enforcement Administration re-classified the schedule of hydrocodone/acetaminophen combination from schedule III of the Controlled Substances Act to schedule II in October 2014, which included tighter controls, such as the prohibition of prescription refills.

To evaluate the effectiveness and net impact of drug policy (the difference before and after policy implementation), quasi-experimental designs, such as before and after comparison and time-series analysis were the approaches recommended by Her Majesty's Treasury in the

UK[181]. According to different research purposes, several studies have applied different designs to evaluate the impact of opioids re-scheduling and withdrawal in the US and the UK[182-185]. Although a pre- and post-historical comparison cohort study was used to assess the impacts of propoxyphene withdrawal on opioid utilisation at an individual-patient level[182], to evaluate the impact on short-term opioid utilisation and long-term trend, time-series analysis is often applied (Table 10)[183-185].

However, limiting the accessibility of opioid analgesics by regulation has been found to be associated with the increased utilisation of other opioids due to substitution effect[183-185]. Although tramadol was classified as a Schedule III controlled drug from June 2014 to control increasing tramadol utilisation and tramadol-related deaths in the UK[33], there was no research evaluating its impact before this PhD study.

Table 9. Summary of studies evaluating the association between tramadol utilisation and serious adverse events in the UK

Authors	Study design	Outcome	Tramadol measure interval	Results
Hershel *et al.* (1998)[169]	Nested case-control	Seizure	90 days after tramadol initiation	No seizure related to tramadol monotherapy.
Gasse *et al.* (2000)[168]	Nested case-control	Seizure	90 days after tramadol initiation	Only 21 cases of seizure were identified, and seizure was not related to tramadol monotherapy.
Fournier et al. (2014)[167]	Nested case-control	Hospitalization for hypoglycaemia	30 days after tramadol initiation	Comparing with codeine users, tramadol users had a significantly higher risk of hospitalization for hypoglycaemia (hazard ratio: 3.6; 95%CI: 1.6-8.3).
Fournier *et al.* (2014)[166]	Nested case-control	Hospitalization for hyponatremia	30 days after tramadol initiation	Comparing with codeine users, tramadol users had a significantly higher risk of hospitalisation for hyponatremia (HR: 2.05; 95%CI: 1.1, 3.9).

Table 10. Summary of studies evaluating the impact of opioid re-scheduling or withdrawal in the US or the UK

Authors	Study design	Outcome	Time interval	Results
Research evaluating the impact of hydrocodone/acetaminophen combination re-schedule in the US				
Jones *et al.* (2016)[185]	Interrupted time-series analysis	The quarterly number of prescribed tablets and prescriptions	October 2011 to March 2015	Although the quarterly number of dispensed hydrocodone combination preparations prescriptions and tablets decreased after reschedule, the quarterly number of prescriptions and tablets for dispensed non-combined hydrocodone preparations increased
Seago *et al.* (2016)[184]	Before and after comparison	The number of prescriptions	July 2014 to January 2015	A decrease in the number of hydrocodone combination preparations, but there was an increase in the number of prescriptions of tramadol and codeine preparations.
Research evaluating the impact of withdrawal of co-proxamol and propoxyphene				
Hawton *et al.* (2009)[183]	Interrupted time-series analysis	Quarterly number of opioid analgesic preparations and suicides	1998 to 2007	The number of suicides by co-proxamol poisoning decreased significantly, and there was no increase in suicides by poisoning of other analgesics. Although the quarterly number of co-proxamol preparations decreased significantly after the implementation of co-proxamol withdrew, the quarterly number of codeine preparations increased significantly.
Hayes *et al.* (2015)[182]	Pre and post-historical comparison cohort study	Opioid discontinuation Chronic opioid use Daily opioid dose	November 2008 to November 2010	10.6% and 26.6% of patients in the policy-affected cohort stopped opioid use and chronic opioid use when compared to 3.8% and 13.5% of patients in the historical comparison cohort. Patients in the policy-affected cohort were 3.2 and 2.7 times more likely to discontinue opioid use and chronic opioid use when compared to patients in the historical comparison cohort.

2.8. Rationale, aim and objectives of this PhD study

This PhD study was initiated by the classification of tramadol as a controlled drug in the UK in 2014. For a medicine with high utilisation and potential risk of serious adverse events, the effectiveness of policy intervention on tramadol utilisation and tramadol-involved opioid-related deaths need to be investigated. Fundamentally, the reasons underpinning the increasing tramadol utilisation must be explored. By studying the reasons for increasing tramadol prescribing, it will help to optimise opioid prescribing and patient's pain management.

Since the definition of opioid-related deaths in the UK is different from opioid-overdose deaths in the US, the evidence derived from epidemiological studies conducted in the US is not optimal to inform the UK clinical practice guidance[5, 19]. However, there is no research in the UK evaluating the association between opioid daily dose and opioid-related deaths. In addition, the published statistics from the UK ONS are based on post-mortem registration which only records information from post-mortem examination [25, 28, 33, 38], and hence potential risk factors, such as patients' demographic characteristics,

history of comorbidity and substance abuse, utilisation of opioids and concurrent sedatives and its association with opioid-related deaths remain unclear in the UK.

In addition, there is no research applying longitudinal data to measure medication utilisation for individual opioid users in the UK, and there is no gold standard to define persistent opioid utilisation for safety evaluation. It is still unclear how patients used opioid persistently and whether any CNS sedatives are involved in the association between prescribing opioids and opioid-related deaths in the UK. To optimise the use of long-term opioid therapy for patients with chronic pain, the impacts of policy implementation, opioid utilisation pattern and safety outcomes associated with persistent opioid utilisation should be studied in order to inform evidence-based practice and further policy making.

Therefore, this PhD applied tramadol as a case study and aims to evaluate policy implementation, opioid utilisation and associated safety outcomes in the UK primary care and the objectives are:

(1) To identify the reasons for increasing tramadol utilisation from individual utilisation patterns and evaluate the effectiveness of tramadol classification on the prevalence of tramadol users, tramadol utilisation and tramadol-related deaths.

(2) To identify patients' characteristics and medicines among cases of opioid-related deaths in the UK.

(3) To evaluate the association between opioid utilisation, including opioid daily dose and persistent opioid utilisation and opioid-related deaths after adjusting for concurrent sedatives.

Chapter 3. Impact of tramadol classification on increasing tramadol utilisation and associated mortality in the United Kingdom

3.1. Introduction

Tramadol is indicated for moderate to severe pain in the UK. In the past decade, the utilisation of tramadol has consistently increased in many countries, including the US, Germany[155] as well as the UK[33]. According to the UK NHS BSA, the annual tramadol utilisation in England increased from 5.9 to 11.1 million DDDs between 2005 and 2012[33]; coincidently, there was a marked increase in the number of tramadol-related deaths during the same period.

In the US, prolonged opioid use for persistent pain has been identified as the main reason for increasing opioid utilisation,[2] although several clinical guidelines[3-5] suggest the long-term opioid use for CNCP remains controversial.[7, 9] However, the reasons attributable to the increasing opioid utilisation, such as tramadol have not been investigated in the UK.

Currently, there is no direct evidence to infer the relationship between increasing tramadol utilisation and related mortality in the UK. At the population level, the NHS BSA only presented tramadol utilisation without adjusting for population size, and tramadol utilisation in Wales was not included in the report;[33] but the published mortality figures from the ONS covered both England and Wales.[28] Consequently, the correlation between tramadol utilisation and tramadol-related deaths has not been established.[33]

Due to the concerns about safety and potential risk of misuse, tramadol was classified as a Schedule 3 Controlled Substance in June 2014 in the U.K.[33] Thereafter, tramadol prescribing needs to follow stricter prescription requirements with clear defined dose and the maximum supply days should not exceed 30 days[33]. For such a medication with high usage and potential harm, the effectiveness of policy intervention on utilisation and tramadol-related mortality is an important public health issue. However, the effect of tramadol classification has not been explored.

3.2. Aim and objectives

This study aimed to develop hypotheses to explain the increasing tramadol utilisation and evaluate policy changes in the UK. The objectives were to (1) identify potential reasons for increasing tramadol utilisation from individual utilisation patterns; (2) evaluate the impact of tramadol classification on prevalence of tramadol users and tramadol utilisation; and (3) explore the trend between tramadol utilisation and tramadol-related deaths.

3.3. Methods

3.3.1. Study design and data source

This cross-sectional study used several data sources which cover information from different geographical region and time frames, including aggregated-level and publicly available data from the UK government sources as well as IPD from a UK primary care database to address multiple research questions and compensate limitation of each database (Table 11).

To explore potential reasons for the increasing tramadol utilisation from individual utilisation patterns, validate findings about the impact of tramadol classification on monthly tramadol utilisation from aggregate-level data and evaluate the impact of tramadol classification on prevalence of tramadol users and tramadol utilisation, a UK primary care database, the CPRD from January 1993 to December 2015 was used after receiving approval from the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (Protocol number: 12_007RA) (Appendix 1).

CPRD is the largest verified primary care database of anonymised clinical records in the UK. IPD in CPRD were prospectively collected from general practitioners' daily records and it represents about 8.3% of the UK population up to March 2016.[186-188] The population is representative of the UK general population in terms of the age and gender distribution, and hence, CPRD has been widely used in drug utilisation research in UK primary care.[189, 190]

Monthly practice-level dispensing data from October 2010 to September 2015 was used as the primary data source to evaluate the impact of tramadol classification on monthly tramadol utilisation in England.[38] To explore the correlation between annual tramadol utilisation and tramadol-related deaths between 2004 and 2015, this study used mortality data which is originally recorded by the International Classification of Diseases-the tenth version (ICD-10) diagnosis codes[28], annual aggregated-level dispensing data from Prescription Cost Analysis (PCA) in England[63] and Wales[191] and the annual number of mid-year population estimates from the ONS[192]. Those aggregate-level data are publicly available and use requires no ethical review.

3.3.2. Study population

For the IPD analysis, adult CPRD registrants (age >18 years) prescribed tramadol between January 2000 and December 2015 were included. For monthly practice-level dispensing data, practices which issued any tramadol prescriptions between October 2010 and September 2015 in England were included.

3.3.3. Outcomes measured using aggregated-level data

The annual number of tramadol-related deaths/100000 inhabitants and annual and monthly DDDs of dispensed tramadol/1000 inhabitants were measured in aggregated-level statistics and datasets. The number of tramadol related deaths was directly extracted from government reports.[28] The annual quantity of tramadol preparations reported in the PCA was used to calculate the annual number of DDDs dispensed in England[63] and Wales[191]. While the quantity of tramadol preparations extracted from monthly practice-level dispensing data were used to calculate the monthly number of DDDs dispensed in England.[38]

Table 11. A summary of aggregated-level data and IPD used in this study

Data source	Dataset	Countries and time	Extract information	Outcome measure
Aggregated-level statistics and datasets				
ONS	Deaths related to drug poisoning[28]	England and Wales, 2004-2015	Annual number of tramadol-related deaths	Annual number of tramadol-related deaths/ 100000 inhabitants
ONS	Annual number of mid-year population estimates[192]	England and Wales, 2004-2015	Annual number of mid-year population estimates	Annual and monthly DDD/1000 inhabitants Annual number of tramadol-related deaths/ 100000 inhabitants
NHS Digital	Annual Prescription Cost Analysis[63]	England, 2004-2015	Annual quantity of dispensed tramadol preparations	Annual DDD/1000 inhabitants
NHS Wales*	Annual Prescription Cost Analysis[191]	Wales, 2004-2015	Annual quantity of dispensed tramadol preparations	Annual DDD/1000 inhabitants
NHS Digital	Monthly practice-level dispensing data[38]	England, October 2010 to September 2015	Monthly quantity of dispensed tramadol preparations	Monthly DDD/1000 inhabitants
Individual patient data				
CPRD	Therapy file	United Kingdom, January 1993 to December 2015	Tramadol prescriptions	Monthly DDD/1000 registrants Monthly incidence and prevalence/10000 registrants Annual supply days and mean daily dose

(Note) ONS: Office for National Statistics, NHS: National Health Service, DDD: Defined Daily Dose, CPRD: Clinical Practice Research Datalink, *NHS Wales Shared Services Partnership

The annual number of tramadol-related deaths was divided by the mid-year number of population in England and Wales and then multiplied by 100000 to calculate the annual number of tramadol-related deaths/100000 inhabitants. The total dose of each tramadol preparation was calculated by multiplying strength (in milligrams) and quantity, and then summed in annual or monthly basis, and then divided by 300 (as defined by the WHO[61]) to calculate the number of DDDs of tramadol. The annual or monthly DDD was adjusted by the mid-year number of population[192] to derive the annual or monthly number of DDDs of dispensed tramadol/1000 inhabitants.

3.3.4. Outcomes measured using individual patient data

The monthly prevalence and incidence of tramadol users/10000 registrants, monthly DDDs/1000 registrants and annual supply days and mean daily dose for each tramadol user were measured by using tramadol prescription records form CPRD.

Adult patients who received their first tramadol prescription during the

study period were identified as new tramadol users in that calendar year, and if the patients received tramadol in the subsequence years, they will be classified as existing users in the subsequence years. The number of new and existing tramadol users were calculated in each calendar month, and adjusted by the total number of active patients in the CPRD to derive the monthly incidence and prevalence of tramadol users/10000 registrants.

The total dose of each tramadol prescription was calculated by multiplying strength and quantity, and then converted to the monthly number of DDDs; which was further adjusted by the number of active patients in the particular calendar month to calculate the monthly number of DDDs of tramadol/1000 registrants.

For each tramadol prescription, the dose was divided by numerical daily dose (recorded by physicians and available in the CPRD therapy file) to derive the number of supply days. If the interval between two consecutive prescriptions was shorter than the supply day of the anterior

prescription, then the supply day was replaced by interval between the two prescriptions.

For each patient, the total doses of tramadol prescriptions and annual number of supply days were summed in each calendar year. If the annual number of supply days was more than 365 days, then it was capped to 365 days. The annual dose was divided by annual number of supply days to derive the annual mean daily dose in particular calendar year.

3.3.5. Data analysis

Descriptive statistics were used to report annual dose and number of supply days. The trend of (1) monthly incidence and prevalence of tramadol users from January 2000 to December 2015; (2) annual mean daily dose stratified by new and existing users; (3) annual number of DDDs of dispensed tramadol/1000 inhabitants and the rate of tramadol-related deaths in England and Wales from 2004 to 2015 were reported graphically. Cross-correlation between the two time-series, i.e.

annual number of tramadol-related deaths/100000 inhabitants and annual number of DDDs of dispensed tramadol/1000 inhabitants, was investigated at no lag time effect and presented as cross-correlation coefficient (ranged from -1 to 1).

Interrupted time-series analysis (ITSA)[193] was used to evaluate the impact of tramadol classification in June 2014 on the levels and trends of two series between October 2010 and September 2015: (1) monthly prevalence and incidence of tramadol users estimated from CPRD; (2) monthly DDD/1000 registrants estimated from both monthly practice-level dispensing data and CPRD. In CPRD, monthly DDD/1000 registrants was further stratified by new and existing users to identify the impact of tramadol classification on different patient groups.

The Durbin Watson test was used to test first-order autocorrelation in each time series, as no first-order autocorrelation was found[194], and hence auto-regressive integrated moving-average (ARIMA) model was not applied in the ITSA[195]. In the regimented regression model, baseline

trend before classification (β_1), change in the level (β_2) and change in trend after classification (β_3) were tested and reported for each time series. Additional time points in the policy development were tested in sensitivity analysis (Appendix 2). All analysis was performed using STATA 14 (Stata-Corp, Texas, USA, 2015).

3.4. Results

3.4.1. Trend of prevalence and incidence of tramadol users from 2000 to 2015

The IPD extracted from CPRD showed that the monthly prevalence and incidence of tramadol users increased from 23 to 99.3/10000 registrants and 4.1 to 7.7/10000 registrants respectively between January 2000 and May 2014 (Figure 6).

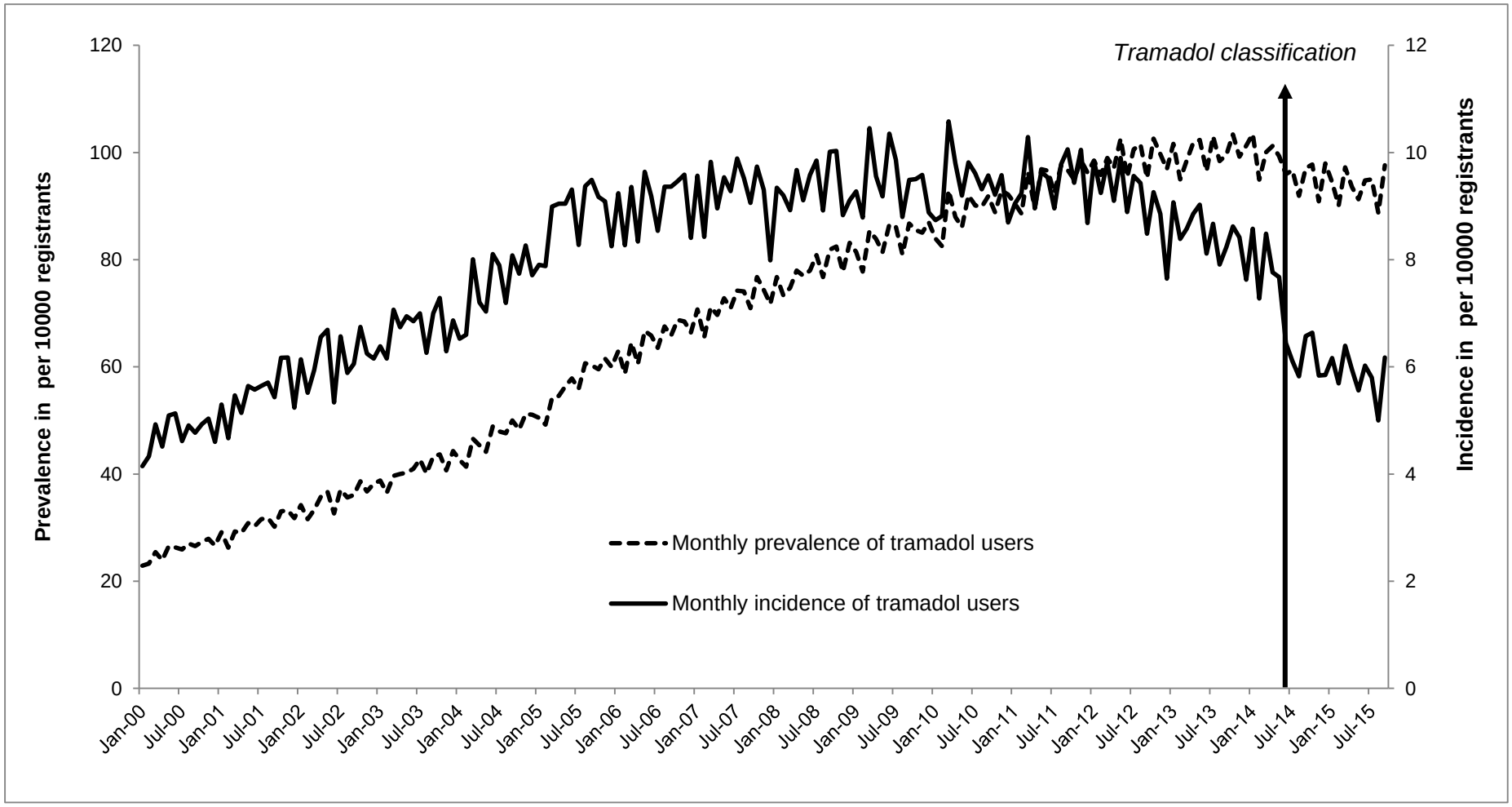
3.4.2. Annual dose, supply days and mean daily dose from 2000 to 2015

For all adult tramadol users in CPRD, most tramadol prescriptions were issued for existing tramadol users. In 2000, 69.2% of the annual tramadol dose was prescribed to existing tramadol users, and this proportion increased to 91.4% in 2015 (Appendix 3). In addition, between 2000 and 2015, the annual dose per existing tramadol user in each calendar year (range: 37910.8 to 40218.2 mg) was consistently higher than the annual dose per new users (range: 9717.8 to 11642.6 mg). Furthermore, the annual supply days per existing tramadol users in each calendar year (range: 134.3 to 150.7 days) was consistently higher

than new users (range: 35.7 to 47.9 days) (Appendix 4).

From 2000 to 2013, the annual mean daily tramadol dose increased in both existing and new users. After 2007, new users had greater annual mean daily dose than existing users, however, since tramadol classification, the annual mean daily dose of new users decreased in 2014 and 2015 (Figure 7).

Figure 6. Monthly prevalence and incidence of tramadol users per 10000 registrants between 2000 and 2015



3.4.3. Impact of tramadol classification on monthly tramadol utilisation

Tramadol classification had similar impacts on its utilisation in the results of ITSA using aggregated-level data and IPD. In the monthly practice-level dispensing data, the ITSA revealed that the level (β_2: -12.9, p=0.017) and the trend (β_3: -1.6, p=0.002) of monthly tramadol utilisation significantly decreased after tramadol classification, despite there was a significant increase in the baseline trend (β_1: 0.79, p<0.001) before tramadol classification (Figure 8).

Similarly, the IPD from CPRD showed a significant increase trend (β_1: 0.56, p<0.001) before tramadol classification, and the level significantly reduced at the launch of classification (β_2: -16.3, p=0.021) but there was no significant change in the trend of tramadol utilisation after classification.

Figure 7. Mean daily dose between existing and new tramadol users

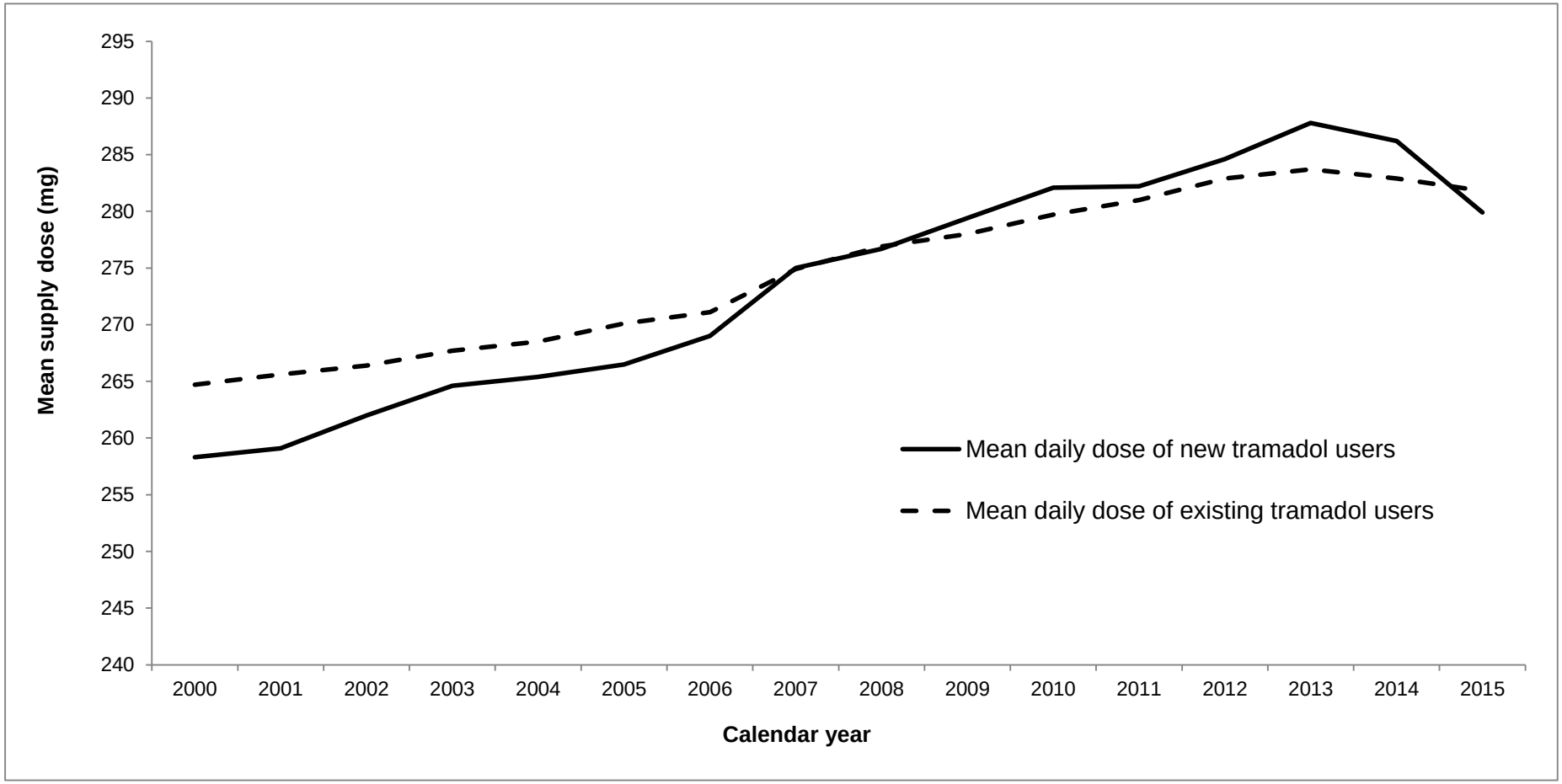
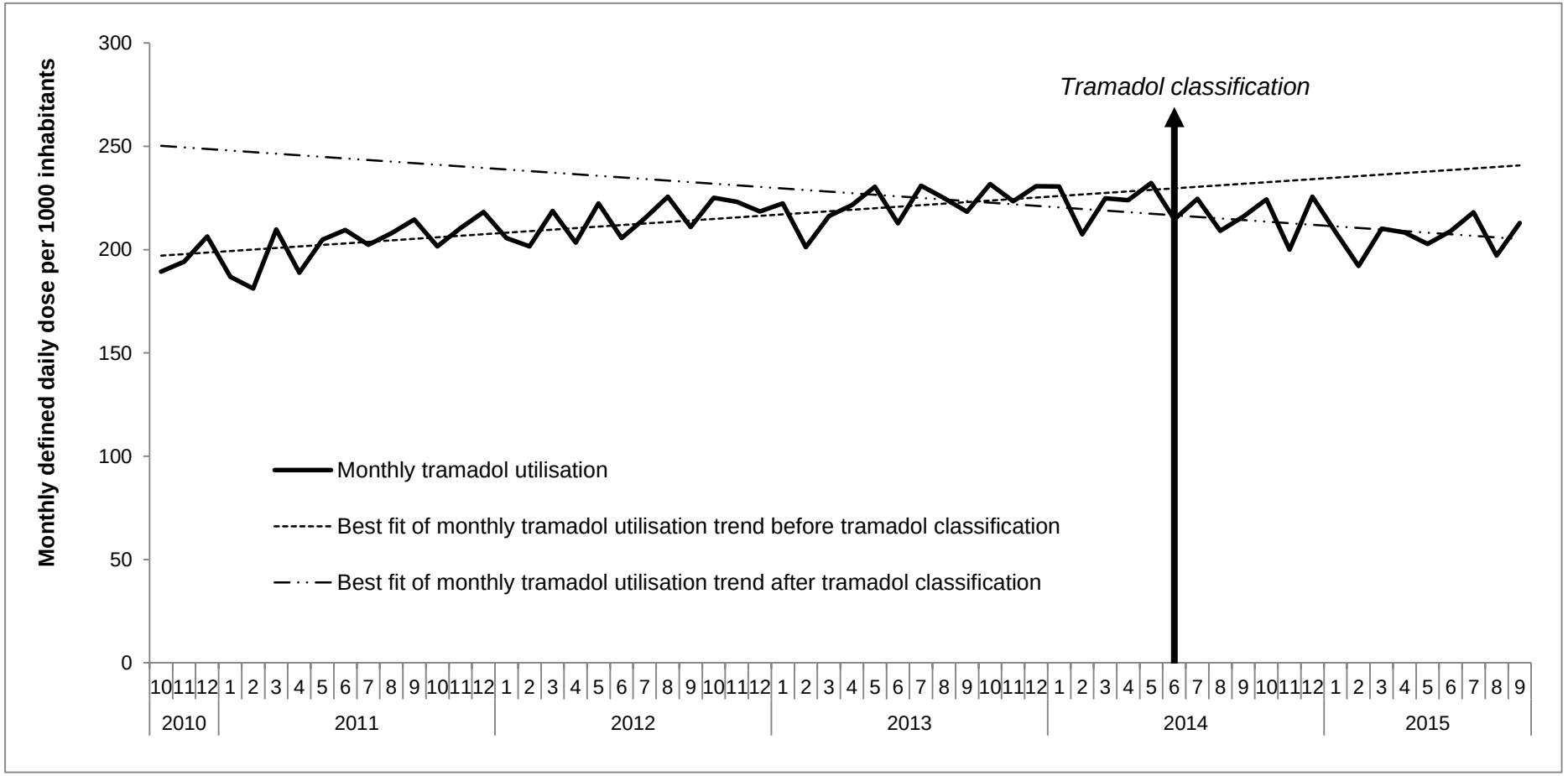


Figure 8. Monthly tramadol utilisation in England between October 2010 and September 2015 in the national practice-level dispensing data



When stratifying monthly tramadol utilisation into existing and new tramadol users, before the classification, the trend significantly increased in existing users (β_1: 0.63, p<0.001) (Figure 9) but decreased in new users (β_1: -0.07, p<0.001) (Figure 10). After the launch of tramadol classification, the level significantly decreased in both existing users (β_2: -13.8, p=0.041) and new (β_2: -2.6, p<0.001) users. However, there was no significant change in the trend of tramadol utilisation for both existing and new users after tramadol classification.

3.4.4. Impact of tramadol classification on monthly prevalence and incidence of tramadol users

In addition to the decrease in monthly tramadol utilisation, tramadol classification also decreased the prevalence of tramadol users. In the IPD from CPRD, the baseline trend significantly increased in prevalence (β_1: 0.21, p<0.001) but decreased in incidence (β_1: -0.04, p<0.001) of tramadol users between October 2010 and May 2014. The level of both prevalence (β_2: -6.4, p=0.001) and incidence (β_2: -1.7, p<0.001) decreased significantly after the launch of tramadol classification. However, only the trend of prevalence decreased significantly (β_3: -0.37,

p=0.028) and there was no significant change in the trend of incidence (Figure 6). All sensitivity analysis models found that other intervention time points had no significant effect on tramadol utilisation, prevalence and incidence.

3.4.5. Trend of annual tramadol utilisation and tramadol-related deaths from 2004 to 2014

Before tramadol classification, the annual tramadol utilisation summarised in PCA in England and Wales increased from 1190.4 to 2714.7 DDDs/1000 inhabitants during 2004 and 2013; meanwhile the number of tramadol-related deaths/100000 inhabitants increased from 0.08 in 2004 to 0.42 in 2014 (Figure 11). After tramadol classification, tramadol annual utilisation decreased, and the number of tramadol-related deaths/100000 inhabitants decreased to 0.36 in 2015. A strong positive correlation was found between tramadol annual utilisation and related deaths (cross-correlation coefficient=0.9090).

Figure 9. Monthly tramadol utilisation for existing tramadol users between October 2010 and September 2015 in the IPD retrieved from CPRD

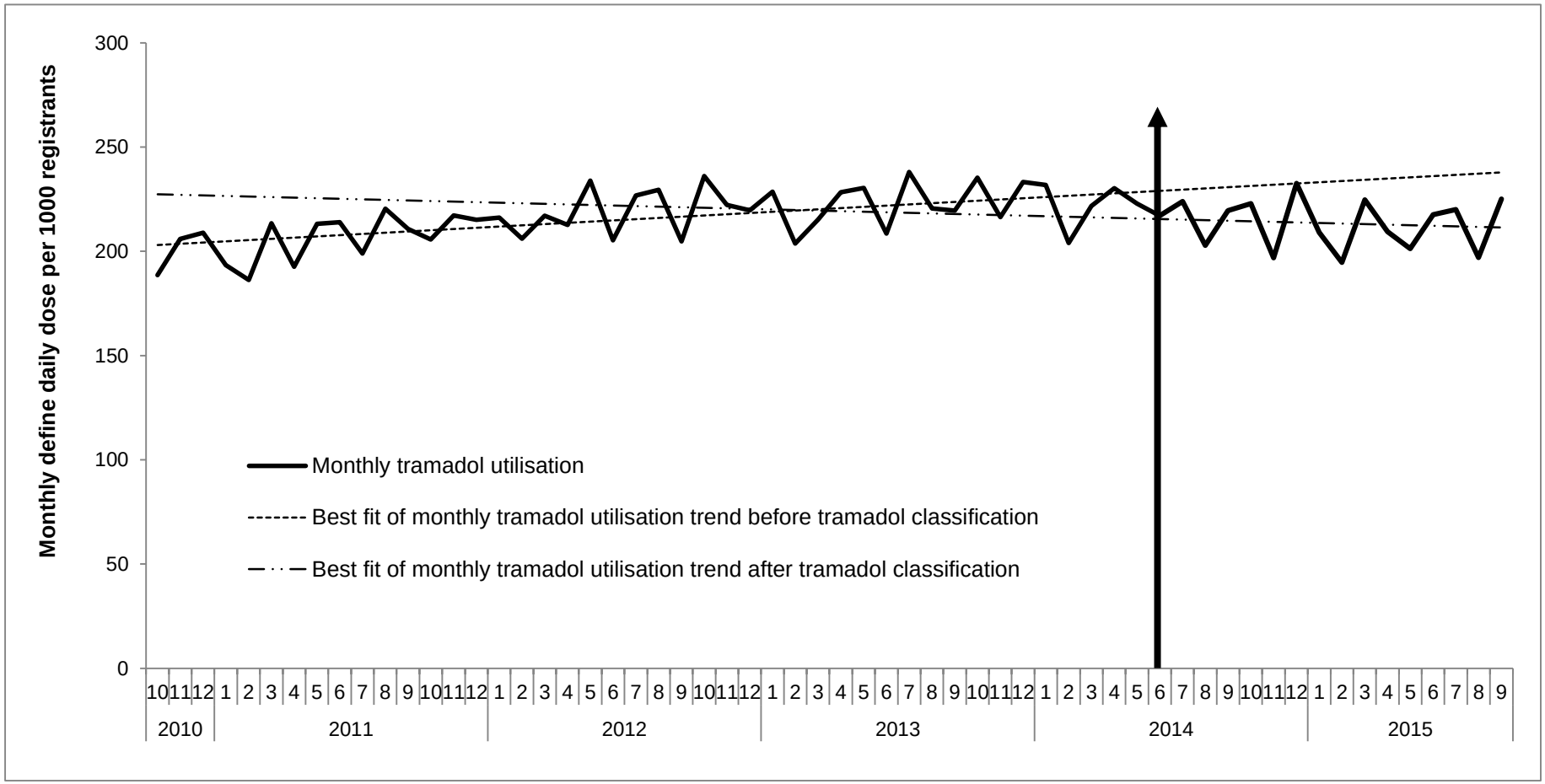


Figure 10. Monthly tramadol utilisation for new tramadol users between October 2010 and September 2015 in the IPD retrieved from CPRD

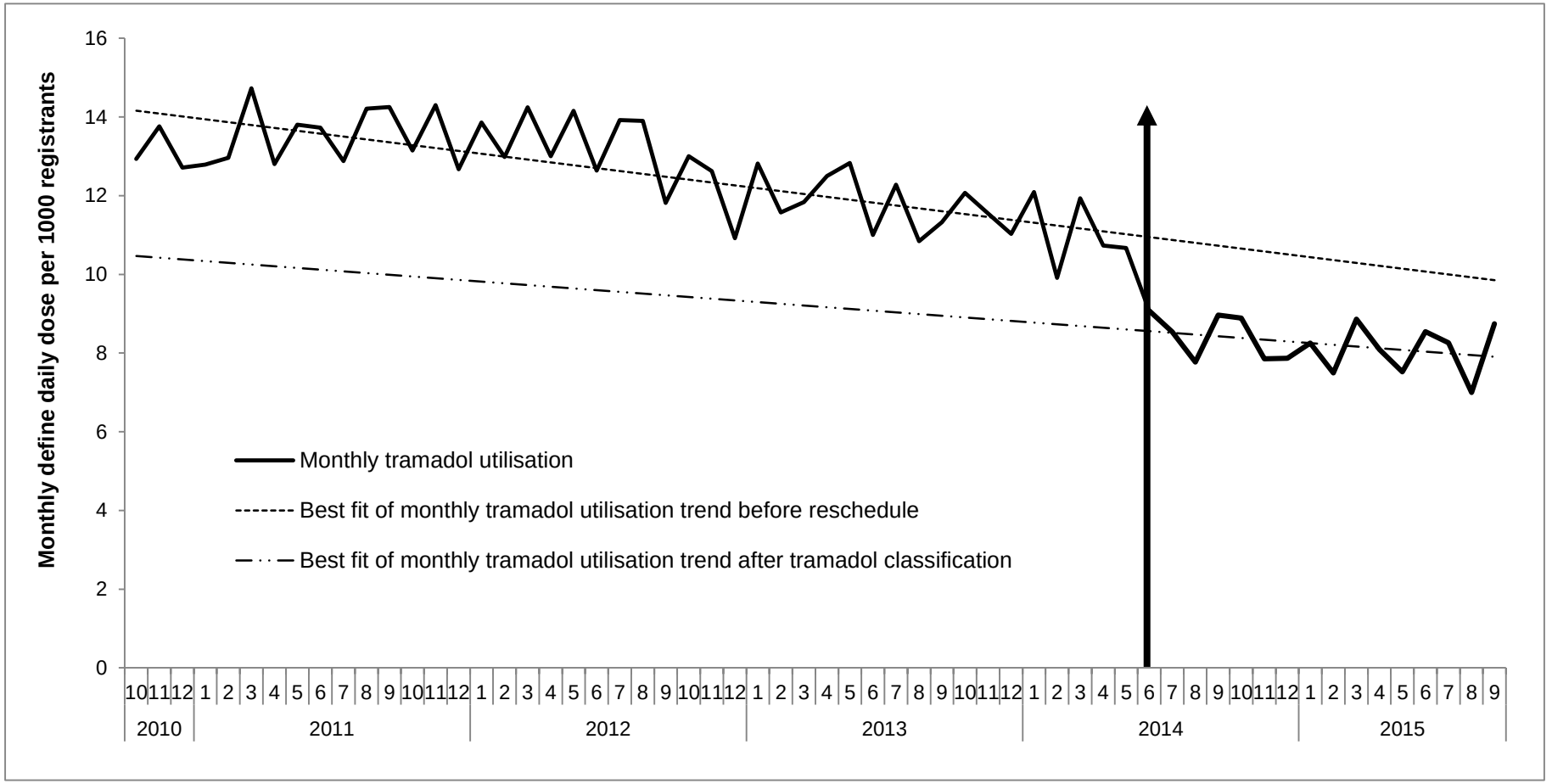
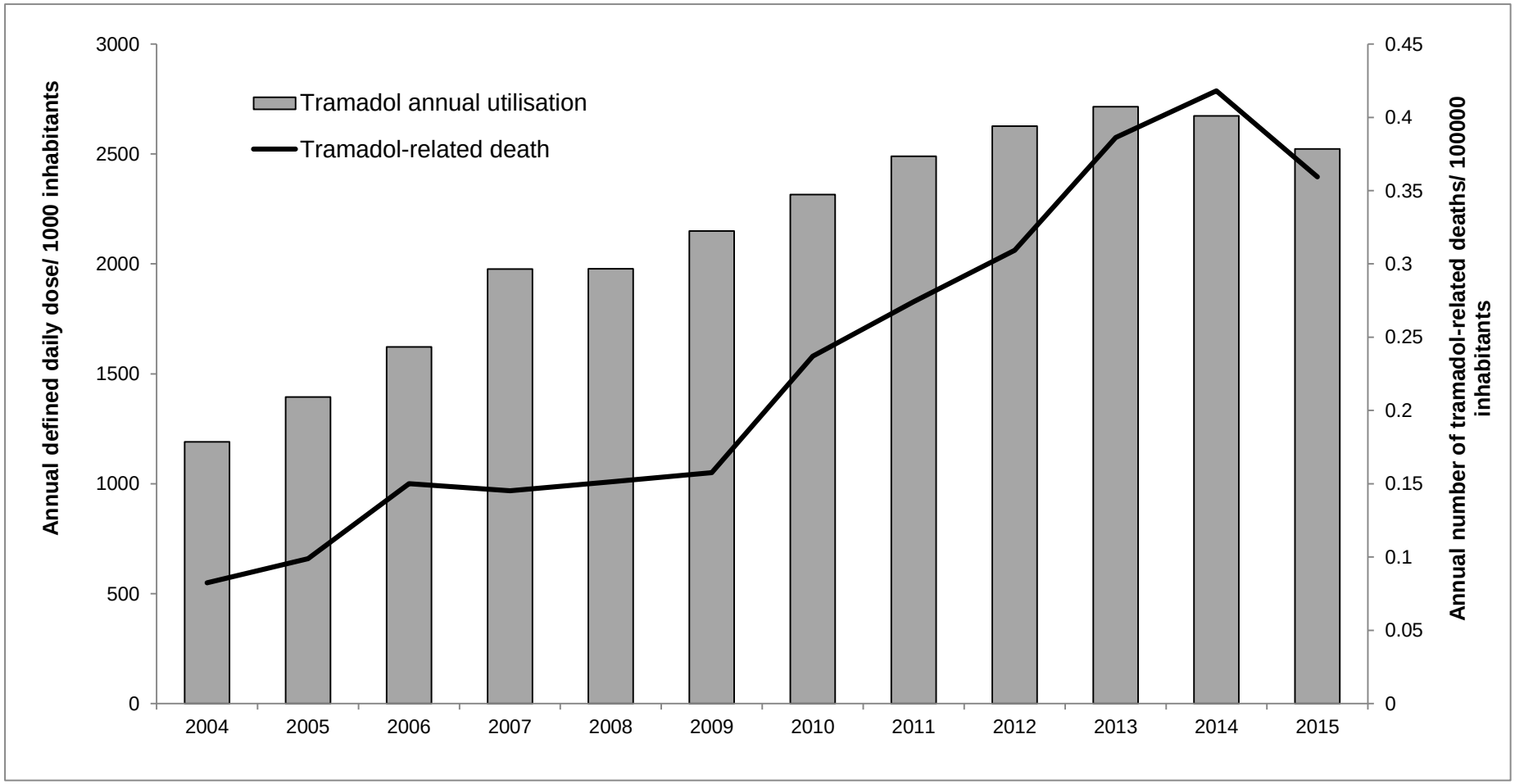


Figure 11. Annual tramadol utilisation and the number of tramadol-related deaths in England and Wales from 2004 to 2015



3.5. Discussion

This study found monthly tramadol utilisation consistently increased before tramadol classification and the increasing trend did not act as a substitution of other more potent opioids because the utilisation of all strong opioids and codeine consistently increased since 2004.[33] Furthermore, the withdrawal of co-proxamol in 2005 did not change the increasing trend of tramadol utilisation and tramadol-related death from 2000.[183]

From the IPD, the monthly incidence of tramadol users doubled and the monthly prevalence increased four-fold per 10000 registrants. The mean daily dose of tramadol prescriptions increased and more than 70% of tramadol users were existing users who had greater number of supply days than new users. Therefore, the increasing prevalence and incidence of tramadol users, higher mean daily dose and the prolonged use of tramadol were the main causes of increasing tramadol utilisation over time.

From the monthly practice-level dispensing data, the monthly tramadol utilisation decreased after tramadol classification. Once tramadol users were stratified into new and existing users in the IPD, the level of tramadol utilisation and the prevalence of tramadol users decreased after classification, but only the trend of prevalence of tramadol users changed significantly after June 2014.

Overall, a similar trend between annual tramadol utilisation and the rate of tramadol-related deaths was found, which is consistent with government publications.[28, 33] In short, after the launch of tramadol classification, monthly prevalence and incidence, overall tramadol utilisation and the number of tramadol-related deaths decreased reversing the upward trend from 2004.

The increasing tramadol utilisation may be attributed to long-term opioid utilisation which is commonly observed in patients with CNCP.[2] In the UK, higher dose and prolonged use of strong opioids was related to increasing demands for pain relief in CNCP.[29] In addition, a

cross-sectional study conducted in Germany found that higher tramadol utilisation was associated with CNCP diagnosis.[155] However, similar to other opioids, there is currently no robust evidence to support the clinical effectiveness of prolonged tramadol utilisation for CNCP.[94, 95, 97, 196] Moreover, evidence from post-mortem toxicological analysis in the UK suggests that tramadol-related deaths were more related to persistent tramadol users.[37, 197, 198]

Nevertheless, the ITSA found tramadol classification did not change the increasing trend of tramadol utilisation in existing tramadol users who had greater number of supply days. In addition, the proportion of tramadol-related deaths in all opioid-related deaths (10.5%) was still higher than codeine-related deaths (6.4%) in 2015, despite more prescriptions for codeine being dispensed.[28]

Although indicators to monitor tramadol related deaths are needed, as tramadol has been considered relatively safe comparing with other strong opioids[9], only one of the previous nested case-control studies

which assessed the association between risk factors and opioid-related deaths included tramadol.[7, 9, 42, 132] Furthermore, tramadol related deaths involved multiple risk factors[37, 197, 198], but there is currently no applicable indicators to monitor tramadol utilisation and related deaths.

In the ITSA, the decreased trend in monthly tramadol utilisation was found in the aggregated monthly practice-level dispensing data but not in IPD. Some reasons might explain the different results derived from the two data sources. First, CPRD contains prescribing records from general practices, but NHS Digital data included community dispensing records, and prescriptions are not necessary always been dispensed. Second, CPRD collects prescription records from selected practices across the UK whereas NHS Digital obtains all dispensing data in England. There might be some variations in patients' characteristics and prescribers' clinical decision making between practices in CPRD and NHS Digital dispensing data. In fact, geographic variation in opioid prescribing has been found in the USA and Australia[199-201], and it was possible that the interpretation and application of policy varied between practices in different regions.

This is the first study to identify the influence of tramadol classification on its utilisation in the UK. To fully explore tramadol utilisation in the past 15 years, several national statistics and datasets as well as CPRD were used to compensate the limitations of each database. We used DDDs to quantify tramadol utilisation which is easy to compare with previous studies and understand the clinical implication as it can be converted into OMEQ by multiplying the potency ratio.[202] Furthermore, to establish hypotheses for further analysis, potential reasons of increasing tramadol utilisation and tramadol-related deaths were identified by measuring both individual and population utilisation.

There are some limitations to this research. CPRD does not included prescription records from secondary care and hence may underestimate tramadol utilisation, especially for acute tramadol use. Tramadol prescriptions outside the study period were not included and hence the new users might be over-estimated. Furthermore, this cross-sectional study aimed to establish potential hypotheses for changes in tramadol utilisation and deaths, but it was not intended to study the causal

relationship between particular utilisation patterns such as chronic use and changes in tramadol utilisation. The number of tramadol-related deaths was an aggregated summary retrieved from government reports and hence characteristics of tramadol-related fatalities were not available to explore.

In conclusion, the prolonged use by existing tramadol users and the increasing prevalence of tramadol users led to increasing tramadol utilisation over the past fifteen years in the UK. Although tramadol classification altered tramadol utilisation and associated deaths, to optimise the use of tramadol in patients with CNCP, future studies are needed to identify the causal relationship between patient characteristics, long-term tramadol utilisation and tramadol-related deaths.

Chapter 4. Measuring the patterns of persistent tramadol utilisation by a multiple-dimension algorithm

4.1. Introduction

Traditionally, tramadol has been considered a relatively safe opioid with a lower risk of addiction and abuse comparing to other strong opioids[31, 32]. In the past decade, there has been a marked increase in tramadol utilisation in many countries, including the US and Germany[155], and tramadol has been the most widely used strong opioid in the UK[33]. Coincidentally, a six-fold increase in the number of tramadol-related deaths was found in the UK[147], and this was attributed to persistent tramadol utilisation, as over 50% of the fatalities were diagnosed with chronic pain[37, 198]. Due to safety concerns and potential risk of abuse, tramadol was re-classified as Controlled Drug and from June 2014[33]. Although there was a significant decrease in tramadol-related mortality and utilisation after tramadol classification, a limited effect on existing users who had a higher number of supply days was found.

'Medication persistence' refers to the continuous use of medicines

during an observed period[203], and it has been found to be associated with improving outcomes in several disease treatments, such as hyperlipidaemia[204, 205]. However, current clinical guidelines[3-5] do not recommend persistent opioid use for CNCP due to a lack of long-term effectiveness and its association with increased risks of emergency department visits, addiction, hospitalisation and mortality[6-9, 206]. In fact, there is currently no gold standard measurement to identify persistent opioid utilisation and monitor its associated clinical outcomes.

In published epidemiological studies, 'prescription gap', 'number of prescriptions' and 'number of days' have been used to investigate the safety associated with persistent opioid utilisation[8, 9, 206]. However, 'prescription gap' only considers the duration of treatment, and it may be not appropriate to examine opioid-related safety issues because the majority of opioid-induced adverse events are dose-dependent. Therefore, dimensions for measuring dose and frequency of opioid use should be considered[7, 9].

Furthermore, applying merely a single-dimension measure in opioid utilisation such as ‘number of prescriptions’ and ‘number of days’ may identify patients with lower opioid dose. Franklin *et al.* (2009) found that the average opioid daily dose in some patients with chronic low back pain is relatively low, even if their opioid prescriptions covered four quarters in a particular patient-year[207]. Therefore, to identify persistent opioid users who regularly take opioids for chronic pain relief and evaluate its associated safety issues, a multiple-dimension algorithm (MDA) composed of measures for frequency and dose of opioid is a better option.

Svendsen *et al.* (2012) had developed a MDA which is a composite of three dimensions including annual dose (AD), annual number of prescription (NP) and annual number of quarters covered with prescription (NQC) for measuring opioid utilisation during the same patient-year[39]. Although several studies have applied this MDA to identify persistent opioid users, the majority of these studies took a cross-sectional approach in Norway to estimate the prevalence of persistent opioid users in a short period of time[39, 40, 103, 208, 209]. None of

them measured opioid persistence from opioid initiation, and no study has investigated the feasibility of applying the MDA to measure the persistence of a single opioid[39, 40, 103, 208, 209].

Studies identifying persistent opioid utilisation have found that persistent utilisation was related to the diagnosis of common psychological illnesses, such as depression and anxiety and substance or drugs abuse disorders prior to opioid initiation[2, 208, 210]. Due to tramadol's dual pharmacological mechanism of action that includes modulation of noradrenaline and serotonin reuptake, tramadol has been prescribed commonly for patients with co-existing depression[154]. Nevertheless, concomitant use of tramadol with antidepressants might induce severe adverse events, such as seizures and serotonin syndrome[159, 169, 211-213]. In order to evaluate the association between persistent tramadol utilisation and its safety outcomes, it is crucial to identify characteristics and medication use related to persistent tramadol utilisation. However, currently, there is no epidemiological study exploring how patient characteristics associated with persistent tramadol utilisation.

4.2. Aim and objectives

Therefore, this study aimed to apply the MDA developed by Svendsen *et al.* in the UK primary care setting to identify persistent tramadol utilisation in patients without a cancer diagnosis and investigate baseline patient characteristics associated with persistent tramadol utilisation.

4.3. Methods

4.3.1. Study design and data source

This retrospective cohort study used a UK primary care database, the CPRD from 1993 to 2011. CPRD is the largest verified primary care database in the UK and collects anonymised longitudinal patient-level clinical records including demographics, clinical diagnoses and prescribing from the UK primary care setting. Up to March 2016, it contains prescribing records and clinical diagnosis from approximately 16 million patients representing about 8.3% of the UK population[186, 188]. The CPRD population is demographically representative of the UK general population[187, 188], and has been widely used for disease or adverse events estimation for individual patients in the UK primary care[214-216]. Therefore, it is an ideal data source for a retrospective cohort study to quantify the long-term use of medicines and investigate the association between prescriptions and patient characteristics. This study protocol was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (Protocol number: 12_007RA) (Appendix 1).

4.3.2. Study cohort selection and data extraction

Patients prescribed with tramadol between 2000 and 2011 were selected and followed from the date of first tramadol prescription (index date) between the 1st of January 1993 and the 31st of December 2011 to death, the end of registration or the 31st of December 2011, whichever comes first.

The procedures to identify the cohort of tramadol users and extract their information was summarised in Figure 12. First, prescription records of tramadol items listed in the British National Formulary (BNF) were identified from product dictionary inbuilt in the “product browser” on the CPRD GOLD online system (Appendix 14); consequently, a list of tramadol product codes representing the prescribed tramadol items was identified. Second, a list of codes representing patients who were prescribed tramadol prescriptions was generated by applying the product codes in the “define tool”. In this step, prescription records before the ‘up-to-standard practice date’ were excluded. ‘Up-to-standard practice date’ is an indicator of irregularities in practices according to mortality rate and continuity in data recording within the practices. Finally,

all patients' records in the relevant files (i.e. patient, clinical and therapy files) of CPRD were extracted via the "extraction tool" in CPRD GOLD by applying the patient's codes.

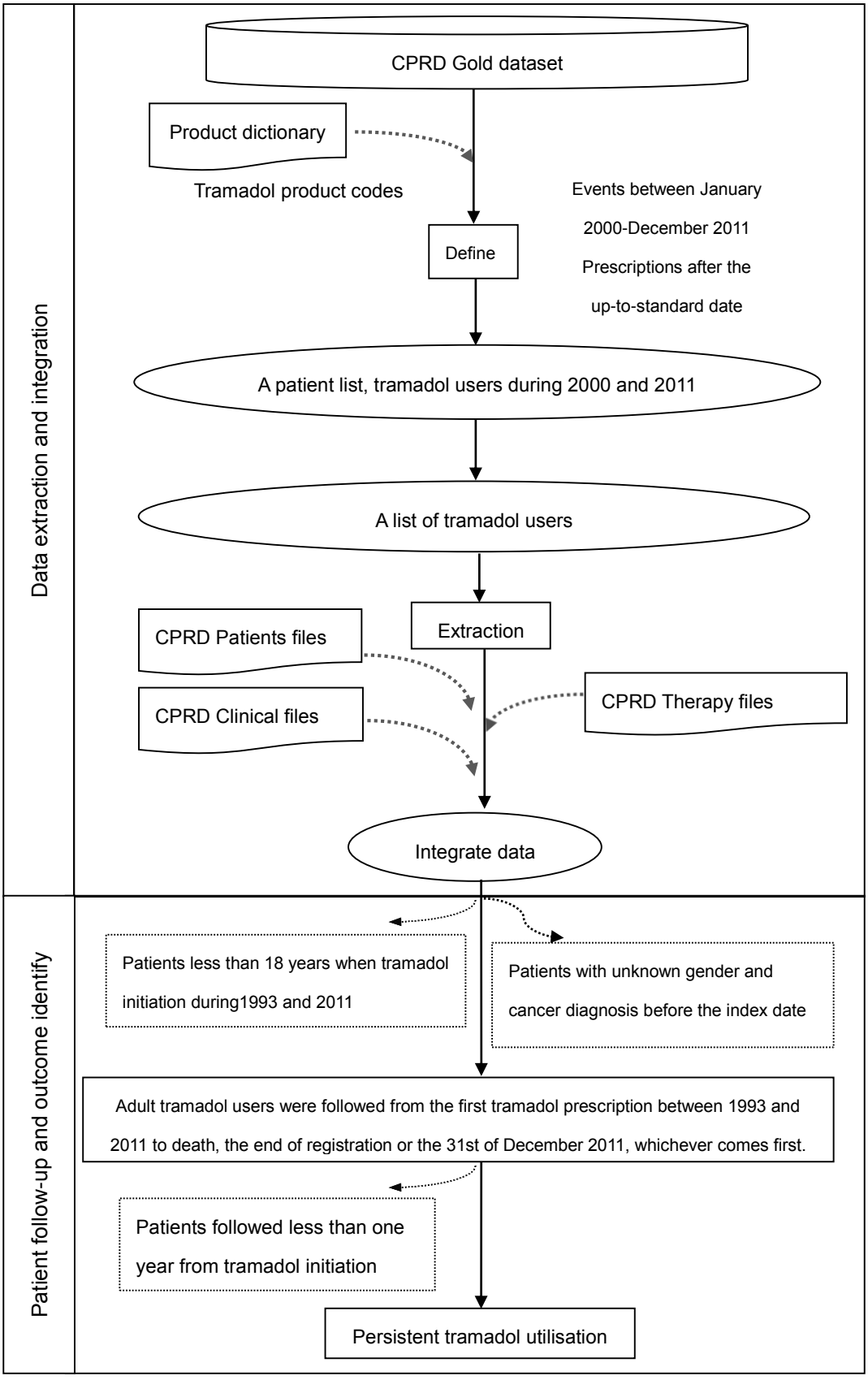
Patients whose gender were recorded as unknown and who were less than 18 years on the index date and had any cancer diagnosis (Appendix 16) before the index date were excluded. In addition, patients whose follow-up period less than one year were also excluded as the minimum duration for defining persistent tramadol utilisation was one patient-year.

4.3.3. Tramadol utilisation measures and definition of persistence

To define persistent tramadol utilisation, for each patient, the 'number of tramadol prescriptions' (NP), 'annual dose' (AD) of tramadol in OMEQ dose and 'annual number of quarters covered with tramadol' (NQC) were measured by patient-year from the index date.

All tramadol prescriptions issued to study cohort during the study period were identified, and the NP for individual patients in each patient-year was calculated. For each tramadol prescription, the dose was derived from multiplying quantity and strength (in milligrams) that recorded in the therapeutic file of CPRD; then the dose was multiplied by 0.3 (the OMEQ-conversion factor of tramadol) to derive OMEQ dose[202]. Although this study only measured the persistence of a single opioid, tramadol dose was converted to OMEQ dose following the original definition of MDA, which consider the potency among opioids[39]. The dose of each tramadol prescription was also divided by daily dose recorded in CPRD to derive the number of supply days.

Figure 12. The procedures to identify tramadol users and extract data



For each patient, if the interval between two consecutive tramadol prescriptions issued dates was less than the number of supply days, then the number of supply day was replaced by the interval between two prescriptions. In each follow-up patient-year, the OMEQ dose of each tramadol prescription was summed to calculate the AD. The NQC was calculated based on the supply day of each tramadol prescription distributed in each quarter of the patient-year.

During the follow-up period, tramadol users were categorised into current persistent tramadol users and non-persistent tramadol users repeatedly in each patient-year. The MDA developed by Svendsen *et al.* (2011) was applied to categorise tramadol users into 'wide' (NQC≥ 3 and AD≥ 4500 mg OMEQ), 'intermediate' (NQC=4 and AD≥ 9000 mg OMEQ) and 'strict' (NQC=4, NP≥ 10 and AD≥ 18000 mg OMEQ) definition groups of current persistent tramadol users in each patient-year[39]. By definition, these three groups overlap, and hence the wide definition group includes both intermediate and strict definition groups, and the intermediate definition group covers the strict definition group.

Persistent tramadol utilisation regarded as the wide definition almost equals to a patient taking at least one tramadol 50 mg capsule (the smallest dosage unit in the UK) per day in a patient-year. The utilisation identified as the strict definition of persistence means that a patient requires at least one tramadol 50 mg capsule every 6 hours or modified release formulation 200 mg per day and regular clinic visits in a patient-year.

In each patient-year, any current persistent tramadol user who was also categorised within the same definition of persistent group in every previous patient-years was defined as a ‘continuing persistent user’; and current persistent tramadol users who were ever categorised within the same definition of persistent group in any of the previous patient-year were identified as a ‘historical persistent user’.

4.3.4. Baseline characteristics of tramadol users

According to literature; patient demographics, medication and disease history before index date that might be associated with persistent

tramadol utilisation were measured in this study[2, 208, 210, 217-219].

Demographic characteristics, including gender and age on the index date were retrieved. Medicines potentially associated with persistent tramadol utilisation, i.e. selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI), TCAs, anticonvulsants, BZDs, z-drug, antipsychotics and other opioids prescribed in six months prior to the index date were measured[2, 208, 217, 218] (Appendix 15 and Appendix 17). Strong opioids included morphine, fentanyl, oxycodone, buprenorphine, hydromorphone, pethidine and tapentadol, and codeine, dihydrocodeine, dextropropoxyphene and meptazinol were categorised as weak opioids. The dose of opioid prescriptions in six months prior to the index date were regarded as a potential indicator of pain intensity in this study. Therefore, opioids that are generally used for managing opioid dependence rather than pain control, such as buprenorphine sublingual and methadone were not measured.

To include the preparations of medicines potentially associated with persistent tramadol utilisation during study period, the product name of each preparation was identified initially by screening the BNF, and all product names were searched on the CPRD online browser.

For each included patient, the prescribed dose of the above medicines was calculated as the number of DDDs, and the prescribed dose of opioids was calculated in OMEQ dose. For transdermal buprenorphine and fentanyl, the strength per hour and the duration were used for total amount calculation. The number of DDDs and OMEQ dose of each prescription was derived from dividing total dose (in milligrams) by the DDD of each medication which is defined by the WHO or multiplying total dose by an appropriate conversion factor of each opioid[61, 202].

Relevant co-morbidities which may be related to persistent tramadol utilisation in the preceding one year before tramadol initiation were identified by read code which was diagnosis code in the CPRD. Psychological illnesses included anxiety, depression, schizophrenia,

panic and post-traumatic stress disorder (PTSD). Chronic pain conditions included low back pain, neuropathic pain, arthritis and fibromyalgia. Alcohol abuse and other substance abuse disorders were also identified[2, 208, 217, 218] (Appendix 16).

For each comorbidity, a group of terms were searched in the column of 'READ term' in CPRD online system to identify relevant codes. As read codes were designed as a hierarchical structure, the read codes in the same level were checked in order to include all the relevant read codes. Finally, read codes applied to record family history or to rule out particular disease were excluded.

4.3.5. Outcome measures

The prevalence of current persistent tramadol users overall tramadol users in each patient-year was calculated and presented according to the three definition groups (wide, intermediate and strict). To explore the pattern of persistence, for current persistent tramadol users in the first patient-year, the proportion of users maintaining persistent utilisation

was calculated from second patient-year onward. Furthermore, the proportion of historical persistent users and continuing persistent users in the current persistent users in each patient-year were also calculated.

4.3.6. Data analysis

Baseline characteristics and pattern of tramadol persistence were reported with descriptive statistics and presented graphically. Logistic regression was used to explore the association between patients' baseline characteristics and being categorised as persistent tramadol utilisation within wide and strict definition group in the first patient-year. This is because the descriptive results suggested that patients persistently used tramadol in the first patient-year tended to use tramadol persistently in the following patient-years. The full model included all potential variables and a parsimonious model which contained particular variables after elimination of non-significant terms was presented. The results were presented as OR and 95% confidence interval (95%CI). All analysis was performed using STATA 14 (Stata-Corp, Texas, USA).

4.4. Results

4.4.1. Baseline characteristics of tramadol users

After excluding patients with unknown gender (n=3), age less than 18 years on the index date (n=2,038, 0.39%) or had any cancer diagnosis before index date (n=48,205, 9.2%), 476,378 tramadol users were identified. Of whom, 92,653 (19.5%) users with less than one-year follow-up (mean±SD: 156.3±111.8 days) were excluded. Overall, 383,725 adult tramadol users with no cancer diagnosis and follow-up for more than one year were included, and the mean and median follow-up duration were 5.2±4.3 and 4.5 years.

The majority of the 383,725 included tramadol users were female (n=233,643, 60.9%) and the mean age of tramadol users at tramadol initiation was 55.7±17.2 years. There were 36.4% (n=139,825) of tramadol users diagnosed with chronic pain conditions, of which, low back pain was the most common diagnosis (27.6%, n=106,076). In addition, 9.1% (n=34,772) and 7.6% (n=28,980) of the cohort had diagnosed records of any psychological illness and depression in one year before the index date.

In six months before tramadol initiation, 8.3% (n=32,044) of users were prescribed opioids, and the majority were prescribed with weak opioids compared with strong opioids (7.8% vs 0.6%). There were 85,154 (22.2%) and 45,067 (11.7%) tramadol users prescribed with antidepressants and BZDs respectively in six months before tramadol initiation (Table 12).

Table 12. Baseline characteristics of tramadol users

Characteristics		All tramadol users n (%)	Non-persistent tramadol users n (%)	Persistent tramadol users n (%)
Number of patients		383725 (100%)	302,311 (78.8%)	81,414 (21.2%)
Follow up time	Mean ±SD (year)	5.2±4.3	5.2±4.2	5.3±4.5
Gender	Female	233,643 (60.9%)	185,531 (61.4%)	48,112 (59.1%)
Age	Mean ±SD	55.7±17.2	55.0±17.3	58.3±16.5
	18≤age<40	76,942 (20.1%)	64,848 (21.5%)	12,094 (14.8%)
	40≤age<65	178,937 (46.6%)	139,902 (46.3%)	39,035 (48.0%)
	65≤age<80	94,152 (24.5%)	72,533 (23.9%)	21,619 (26.6%)
	80≤age	33,694 (8.8%)	25,028 (8.3%)	8,666 (10.6%)
Substance abuse disorder	Alcohol	3,366 (0.88%)	2,390 (0.79%)	976 (1.2%)
	Other substance	1,828 (0.48%)	1,321 (0.44%)	507 (0.62%)
Number of chronic pain diagnoses	0	243,900 (63.6%)	193,111 (63.9%)	50,789 (62.4%)
	1	130,347 (34.0%)	102,253 (33.8%)	28,094 (34.5%)
	More than 1	9,478 (2.4%)	6,947 (2.3%)	2,531 (3.1%)
Chronic pain	Low back pain	106,076 (27.6%)	85,205 (28.2%)	20,871 (25.6%)

	Neuropathic pain	3,051 (0.8%)	2,302 (0.76%)	749 (0.92%)
	Fibromyalgia	1,851 (0.48%)	1,155 (0.38%)	696 (0.85%)
	Arthritis	38,435 (10.2%)	27,558 (9.1%)	10,877 (13.4%)
Psychological illnesses	Any	34772 (9.1%)	26,424 (8.7%)	8,348 (10.3%)
	Anxiety	7,432 (1.9%)	5,756 (1.9%)	1,676 (2.1%)
	Depression	28,980 (7.6%)	21,850 (7.2%)	7,130 (8.8%)
	Panic	2,356 (0.61%)	1,901 (0.63%)	455 (0.56%)
	PTSD	316 (0.08%)	215 (0.07%)	101 (0.12%)
	Schizophrenia	117 (0.03%)	80 (0.03%)	37 (0.05%)
Opioid	Any opioid*	32,044 (8.3%)	24,319 (8%)	7,725 (9.5%)
	Weak opioid	30,028 (7.8%)	22,938 (7.6%)	7,090 (8.7%)
	Strong opioid	2,314 (0.6%)	1,589 (0.5%)	725 (0.9%)
Antidepressants	Any antidepressants	85,154 (22.2%)	61,800 (20.4%)	23,354 (28.7%)
	SSRI/SNRI	46,800 (12.2%)	34,838 (11.5%)	11,962 (14.7%)
	TCA	41,961 (10.9%)	29,269 (9.7%)	12,692 (15.6%)
Antipsychotics	Any antipsychotics	17,018 (4.4%)	12,922 (4.3%)	4,096 (5%)
	First generation	14,600 (3.8%)	11,260 (3.7%)	3,340 (4.1%)
	Second generation	2,773 (0.7%)	1,908 (0.6%)	865 (1.1%)
Anticonvulsants	Yes	9,473 (2.5%)	6,784 (2.2%)	2,689 (3.3%)
BZD	Yes	45,067 (11.7%)	33,964 (11.2%)	11,103 (13.6%)
Z drug	Yes	16,310 (4.2%)	11,863 (3.9%)	4,447 (5.5%)

(Note) SSRI/SNRI: selective serotonin reuptake inhibitor/ serotonin norepinephrine reuptake inhibitors, TCA: tricyclic antidepressants, BZD: benzodiazepine, PTSD: post-traumatic stress disorder, SD: standard deviation

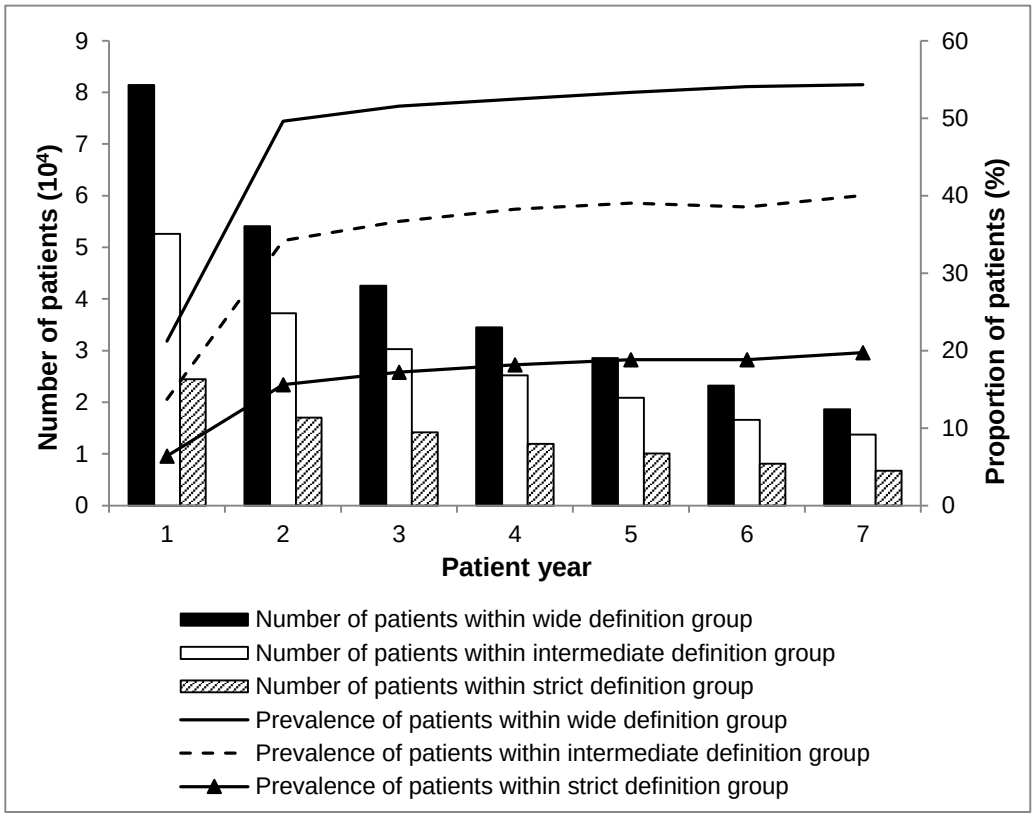
* Strong opioids: morphine, fentanyl, oxycodone, buprenorphine, hydromorphone, pethidine and tapentadol; Weak opioids: codeine, dihydrocodeine, dextropropoxyphene and meptazinol,

4.4.2. Prevalence of persistent tramadol users in each patient-year

Of the 383,725 tramadol users, the prevalence of persistent tramadol

users categorised by wide, intermediate and strict definitions was 21.2% (n=81,414), 13.7% (n=52,613) and 6.4% (n=24,469) in the first patient-year, respectively. For those who received tramadol in the second patient-year, the prevalence of persistent tramadol users categorised by above definitions increased to 49.6%, 34.2% and 15.6% (Figure 13), which were more than double the first patient-year.

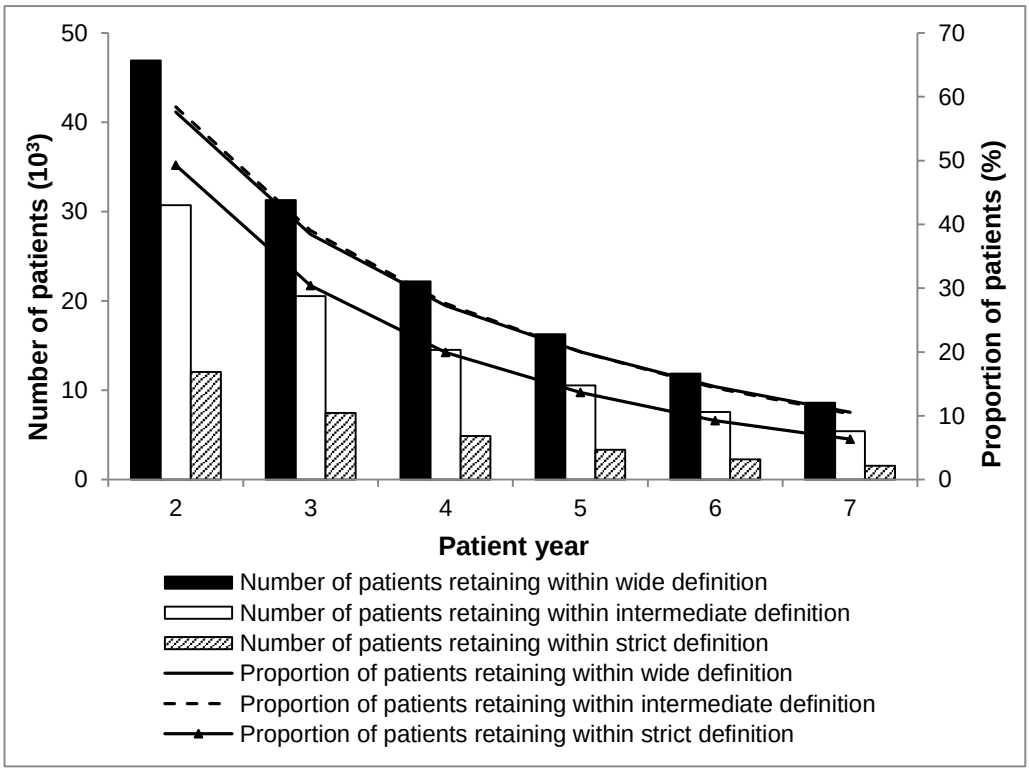
Figure 13. Prevalence of persistent tramadol users categorised by wide, intermediate and strict definitions over all tramadol users in each patient-year



4.4.3. Proportion of continuing persistent users in each patient-year

Of the persistent tramadol users categorised by wide, intermediate and strict definitions in the first patient-year, 57.6%, 58.4% and 49.3% remained in the same group in the second patient-year. Up to the 7th patient-year, 10.5%, 10.3% and 6.3% of persistent tramadol users identified in the first patient-year continuously remained in the same persistent group (Figure 14).

Figure 14. Proportion of persistent tramadol users in the first patient-year who retaining within persistent use in each patient-year



In contrast, of the 302,311 (78.8%) patients who were not persistent tramadol users in the first patient-year, only 2.4% (n=7147) of them were categorised as persistent tramadol users by wide definition in the second patient-year, and 2.4% to 3.1% of all the 302,311 patients were categorised as persistent tramadol users by wide definition during the 3rd to the 7th patient-year.

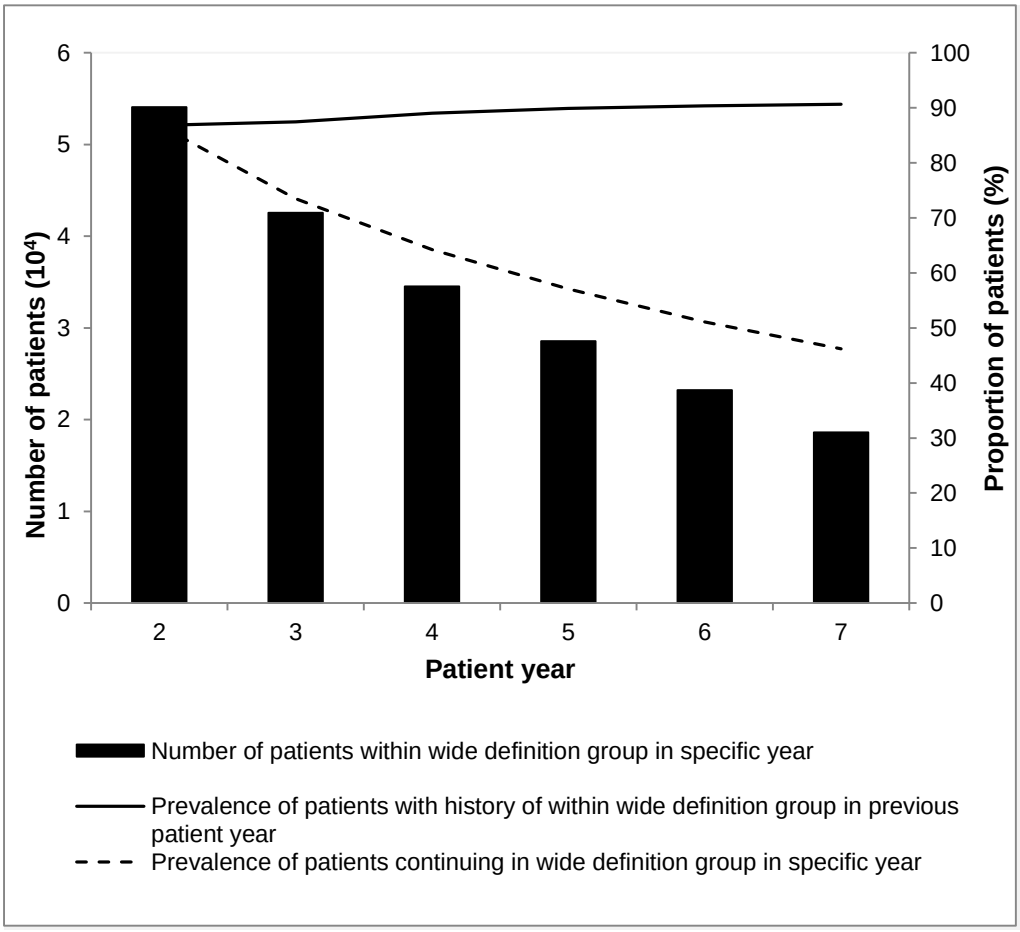
4.4.4. Proportion of current persistent tramadol users with a persistent use history

For persistent tramadol users categorised as the wide definition group in each patient-year, more than 85% were historical persistent users. In the 7th patient-year, 46.2% of persistent users categorised by wide definition were identified as continuing persistent users which means they used tramadol persistently in each patient-year from tramadol initiation (Figure 15).

Furthermore, in each patient-year, more than 71.0% of persistent tramadol users categorised by the strict definition were historical

persistent users; and in the 7th patient-year, 22.9% of persistent users categorised by strict definition were also categorised within the strict definition group annually from the initiation of tramadol.

Figure 15. Proportion of historical persistent users or continuing persistent users in persistent users of each patient-year



4.4.5. Baseline characteristics associated with persistent tramadol utilisation

Several factors identified in the one year prior to tramadol initiation were significantly associated with persistent tramadol utilisation categorised by either wide or strict definitions in the first patient-year, such as male gender (OR: 1.18 and 1.21; all p<0.001), increasing age categories (OR range: 1.41 to 1.79 for wide definition; 1.42 to 1.81 for strict definition; all p<0.001), co-morbidities including alcohol abuse disorder (OR: 1.41 and 1.40; all p<0.001) and substance abuse disorder (OR: 1.22 and 1.46; all p<0.001).

In terms of baseline chronic pain and psychological illnesses, patients diagnosed with fibromyalgia (OR: 2 and 1.79; all p<0.001) and arthritis (OR: 1.42 and 1.37; all p<0.001) were significantly more likely to be categorised into wide or strict definitions of persistent tramadol utilisation, but patients diagnosed with low back pain (OR: 0.89 and 0.84; all p<0.001) were less likely to use tramadol persistently. A diagnosis of PTSD (OR: 1.72 and 1.63; all p<0.001) in the one year before tramadol initiation was significantly associated with persistent tramadol utilisation

defined by wide or strict definitions. However, patients diagnosed with panic disorders (OR: 0.79 and 0.74; all p<0.001) were less likely to be categorised as current persistent tramadol users by both wide and strict definitions (Table 13).

Any BZD, Z drug, second-generation antipsychotic and anticonvulsant prescription prior to tramadol initiation were all significantly associated with persistent tramadol utilisation. Patients taking higher dose of weak opioids (OR range: 1.08 to 4.63 for wide definition; 1.08 to 6.83 for strict definition; all p<0.001), strong opioids (OR range: 1.25 to 2.09 for wide definition; 1.27 to 2.45 for strict definition; all p<0.001), SSRI/SNRI (OR range: 1.13 to 1.45 for wide definition; 1.04 to 1.58 for strict definition; all p<0.001) and TCA (OR range: 1.51 to 2.08 for wide definition; 1.55 to 2.56 for strict definition; all p<0.001) prior to tramadol initiation had an increased odds of being categorised by both wide and strict definitions (Table 13).

Table 13. Association between baseline characteristics with persistent tramadol utilisation in the first patient-year

		Wide definition group	Strict definition group
Patients' characteristics		**OR (95% CI)**	**OR (95% CI)**
Gender	Female	Ref	Ref
	Male	1.18 (1.16, 1.20)	1.21 (1.18, 1.24)
Age	18≤age<40	Ref	Ref
	40≤age<65	1.41 (1.38, 1.44)	1.42 (1.37, 1.48)
	65≤age<80	1.51 (1.47, 1.55)	1.45 (1.39, 1.51)
	80≤age	1.79 (1.73, 1.85)	1.81 (1.72, 1.91)
Alcohol abuse	No	Ref	Ref
disorder	Yes	1.41 (1.31, 1.53)	1.40 (1.25, 1.58)
Substance abuse	No	Ref	Ref
disorder	Yes	1.22 (1.10, 1.36)	1.46 (1.26, 1.70)
Strong opioid[§]	0	Ref	Ref
	0< to ≤1125	1.25 (1.12, 1.41)	1.27 (1.06, 1.52)
	1125< to ≤2250	1.87 (1.52, 2.30)	1.84 (1.36, 2.48)
	2250<x	2.09 (1.71, 2.55)	2.45 (1.89, 3.19)
Weak opioid	0	Ref	Ref
	0< to ≤1125	1.08 (1.04, 1.11)	1.08 (1.03, 1.14)
	1125< to ≤2250	3.89 (3.49, 4.34)	4.28 (3.76, 4.86)
	2250<x	4.63 (3.83, 5.59)	6.83 (5.61, 8.33)
SSRI/SNRI	0	Ref	Ref
	0< DDD ≤90	1.13 (1.09, 1.18)	1.04 (0.98, 1.11)
	90< DDD ≤180	1.32 (1.27, 1.37)	1.29 (1.21, 1.37)
	180<DDD	1.45 (1.39, 1.51)	1.58 (1.49, 1.68)
TCA	0	Ref	Ref
	0< DDD ≤90	1.51 (1.48, 1.55)	1.55 (1.49, 1.62)
	90< DDD ≤180	2.08 (1.97, 2.20)	2.31 (2.14, 2.50)
	180<DDD	2.08 (1.94, 2.24)	2.56 (2.32, 2.83)
BZD	0	Ref	Ref
	0< DDD ≤90	1 (0.97, 1.03)	1.02 (0.98, 1.07)
	90< DDD ≤180	1.41 (1.34, 1.50)	1.51 (1.39, 1.64)
	180< DDD	1.40 (1.32, 1.48)	1.77 (1.64, 1.91)
Z drug	0	Ref	Ref
	0< DDD ≤90	1.12 (1.07, 1.18)	0.99 (0.92, 1.07)
	90< DDD ≤180	1.38 (1.27, 1.49)	1.36 (1.21, 1.52)

	180< DDD	1.33 (1.22, 1.45)	1.55 (1.37, 1.75)
First generation antipsychotics	0		Ref
	0< DDD ≤90		0.97 (0.91, 1.04)
	90< DDD ≤180		1.70 (1.19, 2.42)
	180< DDD		1.58 (0.99, 2.51)
Second generation antipsychotics	0	Ref	Ref
	0< DDD ≤90	1.28 (1.16, 1.43)	1.41 (1.21, 1.64)
	90< DDD ≤180	1.04 (0.86, 1.26)	1.33 (1.03, 1.72)
	180< DDD	1.17 (0.97, 1.42)	1.34 (1.04, 1.72)
Anticonvulsants	0	Ref	Ref
	0< DDD ≤90	1.27 (1.20, 1.34)	1.29 (1.19, 1.40)
	90< DDD ≤180	1.14 (1.02, 1.27)	1.31 (1.12, 1.54)
	180< DDD	1.54 (1.33, 1.77)	1.85 (1.52, 2.24)
CNCP	Low back pain	0.89 (0.87, 0.90)	0.84 (0.82, 0.87)
	Fibromyalgia	2.0 (1.72, 2.08)	1.79 (1.56, 2.06)
	Arthritis	1.42 (1.39, 1.46)	1.37 (1.32, 1.42)
Psychological illnesses	Panic	0.79 (0.71, 0.88)	0.74 (0.61, 0.89)
	PTSD	1.72 (1.35, 2.19)	1.63 (1.13, 2.36)
	Depression	1.07 (1.04, 1.11)	
	Anxiety		1.14 (1.03, 1.25)

A parsimonious model which contained particular variables after elimination of non-significant terms was presented.

OR: odds ratio, CI: confidence interval, DDD: Defined daily dose, SSRI/SNRI: selective serotonin reuptake inhibitor/ serotonin norepinephrine reuptake inhibitors, TCA: tricyclic antidepressants, BZD: benzodiazepine, PTSD: post-traumatic stress disorder, CNCP: chronic non-cancer pain, Ref: reference

[§]Strong opioids: morphine, fentanyl, oxycodone, buprenorphine, hydromorphone, pethidine and tapentadol; Weak opioids: codeine, dihydrocodeine, dextropropoxyphene and meptazinol

*Consumption of opioid was presented by OMEQ

4.5. Discussion

The MDA developed previously to identify persistent opioid utilisation is also able to identify persistent tramadol utilisation. Although only 20% of users were prescribed with tramadol persistently in the first patient-year, once patients received tramadol from the second patient-year, half of them used tramadol regularly. On the other hand, despite a high proportion (more than 85%) of persistent tramadol users having a history of persistent tramadol utilisation, only 10% of them continuously retain in persistent utilisation up to the seventh patient-year. This implies that the persistence of tramadol utilisation followed the nature of chronic pain which is an intermittent and recurrent pattern and this pattern should be considered when evaluating its associated safety.

Although this study only measured persistence of a single opioid instead of entire opioid class, we found a similar pattern of persistence between this study and published studies measuring opioid persistence. Several studies conducted over a shorter study period (3 to 6 years) than this study have applied MDA to measure the persistence of the opioid class rather than single opioid in Norway[39, 40, 103, 208, 209]. Similarly, those

studies found that once patients used opioids persistently in the first patient-year, there is a tendency that they will be persistent opioid users in the future[39, 40] and only 68% of persistent opioid users in the first year continuously remained in persist utilisation up to the third year[39]. Furthermore, Mellbye *et al.* (2016) found that more than 60% of persistent users also used opioids persistently in the previous years[40]. Those results imply that the pattern of persistence of opioids is also intermittent and recurrent, similar to the findings from this study, even we followed single opioid users for a more extended period.

Furthermore, patient's baseline characteristics found to be associated with persistent tramadol utilisation in this study were consistent with baseline characteristics related to persistent opioid utilisation that have been identified by either a single dimension measure in the US[210, 219] or the MDA developed by Svendsen *et al.*[208] in several cohort studies. Moreover, Tholen *et al.* (2012) conducted a cross-sectional approach using claims data to identify high tramadol annual dose in Germany in 2007, the results showed that high utilisation of tramadol was associated with patients' characteristics during the prescribing period, such as

increasing age, opioid consumption and history of depression and substance abuse[155]. Although Tholen *et al*. took a different study design, the factors associated with high tramadol utilisation are consistent with this study.

In addition to the persistence of opioids, concomitant medicines can also attribute to opioid-related adverse events. A higher dose of opioids and BZDs have been found associating with opioid-overdose deaths[7, 9, 42]. Besides, about 70% of tramadol-related fatalities in England and Wales were reported to involve alcohol, antidepressants, other opioids and BZDs[25], and more than 40% of fatalities had misused drugs or other substances[37]. A study conducted by Mellbye *et al.* showed that persistent opioid users were more likely to continue concomitant use of BZDs or z-hypnotics than general opioid users[103] and increasing annual opioid prescriptions was also in conjunction with the concomitant use of antidepressants[104].

However, this study only identified the association between persistent

tramadol utilisation and baseline patients' characteristics and did not follow the concomitant medicines during the study period. Concomitant medicines are a critical concern when evaluating the safety of persistent tramadol utilisation, but currently, the utilisation of concomitant medications was still unknown for persistent tramadol users in the UK.

In contrast to previous publications that measured the prevalence and persistence of persistent tramadol utilisation by other methods[155-157, 220], this is the first study to use multiple dimensions in medicine utilisation to identify patients who likely take tramadol regularly for pain relief by longitudinal prescribing data. Although several publications also applied a MDA to identify persistent opioid utilisation[39, 40, 103, 208, 209], this is the first study to follow new users in primary care and estimate a long-term propensity of persistent tramadol use, and hence, it provides information about the pattern and persistence of persistent tramadol utilisation from tramadol initiation. Compared to a previous cross-sectional study that explored the association between high annual tramadol dose and patients' characteristics[155], the temporal relationship between persistent tramadol utilisation and baseline patients' characteristics is explained

better in this study.

There are some limitations to this study. Since CPRD does not include prescriptions from secondary care, the prevalence of persistent tramadol utilisation might be underestimated. However, as tramadol is mainly used for acute pain or surgery in secondary care, the influence on the prevalence of persistent utilisation might be small. Furthermore, CPRD is a secondary database including prescriptions from physicians, and the estimation of tramadol persistence in this study was based on the assumption that patients take medications exactly as prescribed. In addition, pain intensity and physical activity are not recorded in CPRD, and these characteristics might influence the association between persistent tramadol utilisation and patient characteristics. Nevertheless, opioid prescriptions before tramadol initiation were considered in the regression model and it could be a potential indicator of pain severity.

In conclusion, a MDA can be applied to identify persistent tramadol utilisation, and the pattern of persistent tramadol utilisation among

persistent tramadol users is intermittent and recurrent. Although opioid daily dose has been shown related to opioid-overdose deaths[7, 9, 42, 132], currently, there is no gold standard to monitor persistent opioid as well as tramadol utilisation and clinical outcomes associated with persistence. Since tramadol users could combine or switch to other strong opioids when their pain condition progresses, to evaluate the safety of persistent tramadol utilisation, both baseline medications and time-dependent concomitant medications, such as other opioids need to be measured. Further studies need to consider the pattern of persistent tramadol utilisation to validate the MDA by building the association between safety outcomes and persistent tramadol utilisation and adjusting for baseline characteristics and time-dependent concomitant medications.

Chapter 5. Utilisation of concurrent sedatives between persistent and non-persistent opioid users

5.1. Introduction

The majority of serious opioid-related adverse events, such as respiratory depression and oversedation, involved the μ-opioid receptor and there is a dose-response relationship for these effects[48]. Therefore, high opioid dose and the combination of opioids and sedatives that induced respiratory depression have been associated with opioid-related harms, and any opioid working on μ-opioid receptor should be considered when evaluating the safety of prescribing opioids.

To achieve adequate pain relief, switching between different opioids due to lack of effectiveness and undesirable side effects has been suggested by prescribing guidance[5]. In a follow-up cohort study using CPRD, 69.6% and 62.6% of tramadol users with osteoarthritis and chronic low back pain combined or switched to other analgesics, such as opioids, before the 60th day after tramadol discontinuation in a one-year follow-up period[157]. The results from the previous cohort study (Section 4.4.1,

Page 127) also showed that 8.3% of tramadol users were prescribed other opioids within six months before tramadol initiation which implied a proportion of tramadol users possibly combined tramadol with other opioids during tramadol initiation.

Consequently, it is possible that non-persistent tramadol users received other opioids with higher dose and duration after tramadol initiation in order to achieve adequate pain relief. Although Gore *et al.* (2012) have followed and described the combination and switching of opioids for tramadol users[157], there was no research in the UK exploring the use of other opioids for tramadol users, and the difference between persistent and non-persistent tramadol uses for more than one year.

In England and Wales, the number of opioid-related deaths increased from 2012 to 2015 which was paralleled by the increase in opioid prescribing related to persistent use for chronic pain [25, 28, 29]. However, the majority of epidemiologic studies evaluated the safety of prescribing opioids in North America did not include all prescribed opioids that were

available to be prescribed even though all opioids working on μ-opioid receptor should be considered. In fact, tramadol was not included in the majority of studies as tramadol was not a controlled substance before June 2014, and has traditionally been seen as relatively safe compared to other strong opioids[31, 32] and was less likely reported involving opioid-overdose deaths in North America[127, 130, 221, 222]. Currently, an UK-based epidemiology study is needed to evaluate the association between opioid-related deaths and persistent opioid utilisation. Although a MDA has been shown feasible to identify persistent utilisation of a single opioid in Chapter 4, the feasibility of applying a MDA to measure persistent utilisation of multiple opioids is unclear in the UK general practices[39].

In order to quantify the association between opioids and opioid-related deaths, in addition to prescribed opioids, confounding factors, such as concurrent sedatives were also needed to be considered[223]. In addition to physical pain, persistent pain also induced psychological illnesses[10] and medicines for depression, anxiety and insomnia are often indicated to patients prescribed with opioids for persistent pain[11, 12]. Therefore,

persistent opioid users are more likely to be prescribed CNS depressants in pharmacoepidemiological studies[9, 103-105].

Although co-medication might improve physical symptoms and psychological illness and hence reduce the opioid dose[11], the combination of opioids and CNS depressants, such as BZDs, gabapentin and antidepressants, increase the risk of oversedation due to drug-drug interaction[13], and several US epidemiological studies have shown an increased risk of opioid-overdose deaths when opioids are co-prescribed with CNS sedatives such as BZDs and gabapentin[9, 25, 41-44].

Several definitions have been applied to quantify co-medications in order to match different research purpose. Although an association between persistent opioid utilisation and the combination use of sedatives was concluded in the previous publications[9, 103-105], the definition of persistent opioid use and combination use of sedatives were different from the purpose of this PhD study which aims to evaluate the

association between opioid-related deaths and concurrent use of opioids and sedatives.

According to different research purposes, Tobi *et al.* (2007) summarised patterns of co-medications from published literature and categorised them as ‘co-prescribing’, ‘concomitant medication’ and ‘concurrent use’, according to the number of prescriber, whether there was an overlap in prescribing and time of prescribing (Table 14)[224]. In contrast with ‘co-prescribing’ which was applied to evaluate the quality of prescription and ‘concomitant medication’ which was used to identify comorbidity, the definition of ‘concurrent sedative’ was recommended to be applied when evaluating the safety of drug-drug interaction[224].

Although several epidemiological studies aimed to estimate the prevalence of combination use of opioids and sedatives, persistent opioid users were defined by ‘number of prescriptions’ and ‘number of days’ rather than a MDA[9, 104, 105]. In addition, although the cross-sectional study conducted by Mellbye *et al.* (2012) applied a MDA

to define persistent opioid utilisation[39, 103], they aimed to describe the prevalence of concomitant sedatives for persistent opioid users rather than identify potential drug-drug interaction and hence the definition of 'concomitant medication' rather than 'concurrent use' which defined by Tobi *et al.* (2007) was applied[224]. Currently, there is no research applying a MDA and 'concurrent use' to define persistent opioid utilisation and follow concurrent sedatives in the UK.

Table 14. Summary of the definitions of co-medications in published literature

Taxonomy	Research purpose	Same prescriber	Overlap	Day of prescribing	Example
Co-prescribing	Evaluate the quality of prescribing	Yes	Yes	The same day	The prescribing of laxatives together with opioids in order to relieve opioid-induced constipation
Concomitant medication	Apply medication as indicators of patients' comorbidity or disease severity	Not necessary	Yes	Not necessary on the same day	Used the prescriptions of metformin to estimate the prevalence of diabetic among opioid users when diagnosis records were not available.
Concurrent use	Judge causality of safety related to drug-drug interaction	Not necessary	Not necessary	Apart from a defined number of days	The prescribing of proton pump inhibitors within 7 days after warfarin prescription exhausted

(Note) The definitions of co-medications summarised in the review conducted by Tobi *et al*. (2007) [224]

5.2. Aim and objectives

This chapter aims to test the utilisation of opioids other than tramadol between persistent and non-persistent tramadol users and the utilisation of concurrent sedatives between persistent and non-persistent opioid users in the UK primary care setting. The objectives of this chapter are to: - (1) investigate the difference in prevalence, duration and daily dose of opioids other than tramadol between persistent and non-persistent tramadol users in each patient-year; (2) explore feasibility of applying a MDA to define persistent opioid users in the UK primary care settings; (3) identify the difference in prevalence, cover rate and daily dose of concurrent sedatives between persistent and non-persistent opioid users in each patient-year.

5.3. Methods

5.3.1. Study design and data source

This retrospective cohort study used a UK primary care database, the CPRD from 1987 to 2015. The CPRD collected longitudinal clinical records for individual patients from general practitioners' daily records which contain demographics, clinical diagnoses and medical procedure including prescribing. Hence, several drug utilisation research has applied CPRD to explore longitudinal utilisation of medications for individual patients in the UK primary care[189, 190]. The study protocol was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (Protocol number: 12_007RA)

5.3.2. Study cohort and data extraction

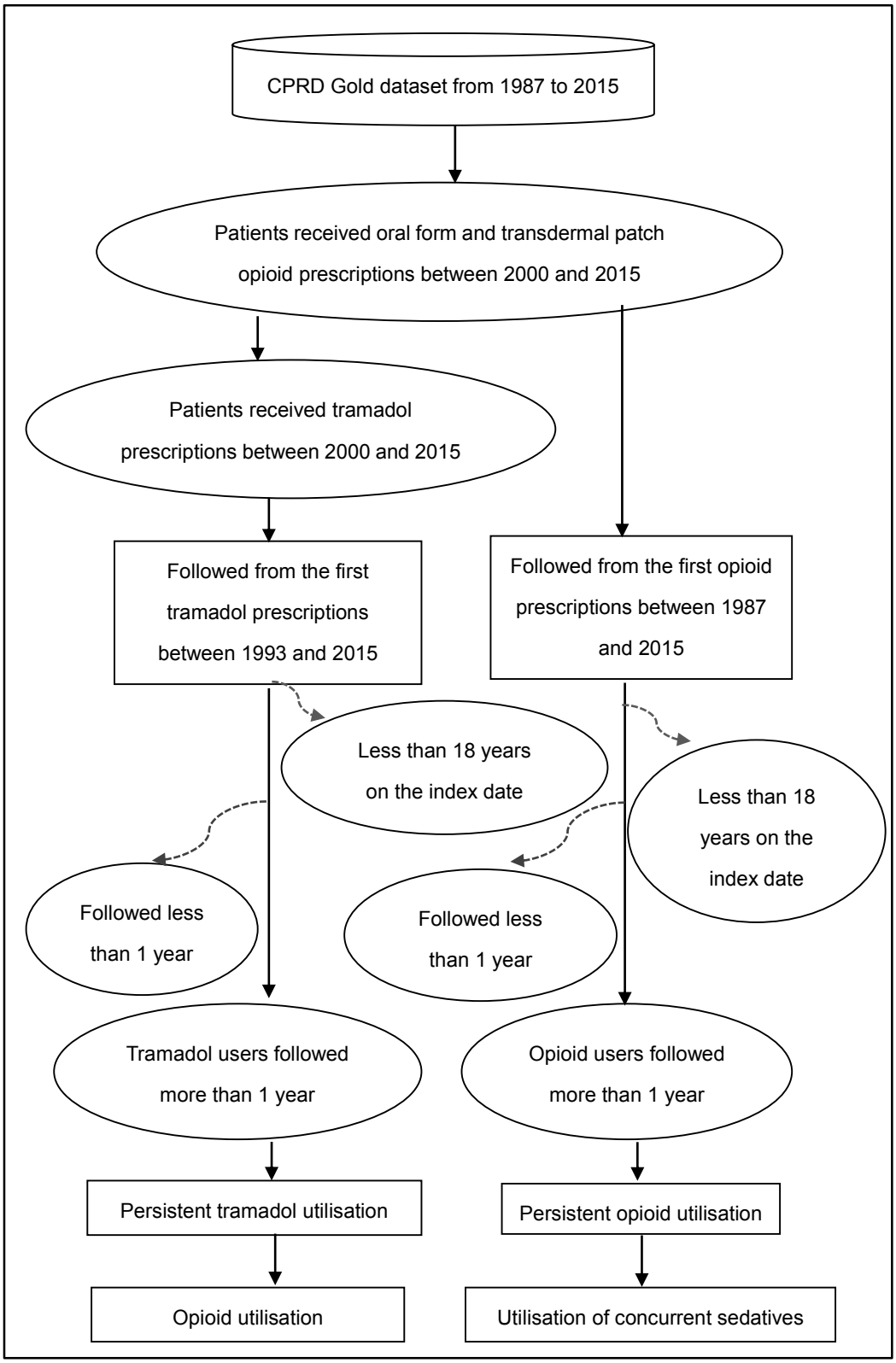
In order to identify the difference in the utilisation of concurrent sedatives between persistent and non-persistent opioid users, opioid users were identified. An additional subcohort of tramadol users was identified from opioid users to test the difference of utilisation of opioids other than tramadol between persistent and non-persistent tramadol users.

The procedures to extract information of study cohort was similar to the procedure mentioned at Section 4.3.2 (Page 117). Prescription records of opioid items listed in the BNF were identified from product dictionary on the CPRD GOLD online system (Appendix 15); consequently, a list of opioid product codes was used to identify patients who were prescribed opioid prescriptions by the “define tool”. In this step, prescription records before the ‘up-to-standard practice date’ were excluded, and a list of patient codes was used to extracted clinical records from relevant files of CPRD via the “extraction tool” in CPRD GOLD.

Patients received prescriptions for oral and transdermal opioid formulations between 2000 and 2015 were selected as opioid users and followed from the date of first opioid prescription between 1987 and 2015 (index date) to death, the end of registration or end of the study period, whichever came first. Adult opioid users (more than 18 years on the index date) with identifiable gender and followed more than one year were included as study cohort as the minimum duration for measuring persistent opioid utilisation was one patient-year (Figure 16).

In order to explore utilisation of opioids other than tramadol for tramadol users, a subcohort included patients who received tramadol between 2000 and 2015 and were followed from the date of first tramadol prescription between 1993 and 2015 (index date for this subcohort) to death, the end of registration or end of study period, whichever comes first. Adult tramadol users (more than 18 years on the index date) with identifiable gender and followed more than one year were included (Figure 16).

Figure 16. Research framework and the process of study cohorts selection



5.3.3. Persistent opioid users and persistent tramadol users

A MDA developed by Svendsen *et al.* (2011) was applied to categorise opioid users and tramadol users into persistent opioid users and persistent tramadol users in each patient-year[39]. Persistent opioid/tramadol users were defined as patients with the number of quarters covered with opioid/tramadol prescriptions equal or more than 3 and annual dose equal or more than 4500 mg OMEQ dose in each patient-year. Detailed information about the definition of persistent opioid/tramadol utilisation has been described in Chapter 4 (Section 4.3.3, Page.118).

5.3.4. The utilisation of other opioids for tramadol users in each patient-year

For tramadol users, the annual number of supply days and the annual mean daily dose of other opioids were measured in each patient-year. Oral and transdermal formulations of other opioids that are not used for managing opioid dependence were identified. Buprenorphine sublingual and methadone which were mainly indicated for opioid substitution therapy rather than pain relief in the UK were not included as the change

in the number of methadone-related deaths was related to the wider adoption of opioid substitution treatment rather than increasing prescribing in the UK[135, 138, 139, 225]. Based on the potency in BNF, codeine, dihydrocodeine, dextropropoxyphene and meptazinol were categorised as weak opioid and fentanyl, morphine, oxycodone, buprenorphine, hydromorphone, pethidine and tapentadol were strong opioids. Opioid preparations with instant release formulation were classified as short-acting formulations, and controlled release, modified release and transdermal patch were categorised as long-acting formulations. Therefore, each opioid prescription was categorised into four categories, short-acting form weak opioid, short-acting form strong opioid, long-acting form weak opioid and long-acting form strong opioid.

For each opioid prescription excluding tramadol, the dose was derived from multiplying quantity and strength (in milligrams) that recorded in the therapeutic file of CPRD and then the dose was multiplied by OMEQ-conversion ratio to derive OMEQ dose to standardise for the potency of individual opioids[202]. In each patient-year, the total OMEQ dose was summed up in annual based to derived annual OMEQ dose

for each category of opioid.

For each opioid prescription, the number of supply days was calculated by dividing dose by numerical daily dose recorded in the therapy file of CPRD. The number of supply days was replaced by the interval between the two consecutive prescriptions of the same category of opioid if the interval between the dates of two consecutive prescriptions was shorter than the supply day.

In each patient-year, the number of supply days was summed up on an annual basis to derive the annual number of supply days for each category of opioid. The annual number of supply days for each category of opioid was replaced by 365 days if it is greater than 365 days. The mean daily OMEQ dose was calculated by dividing annual OMEQ dose by the annual number of supply days for each category of opioid.

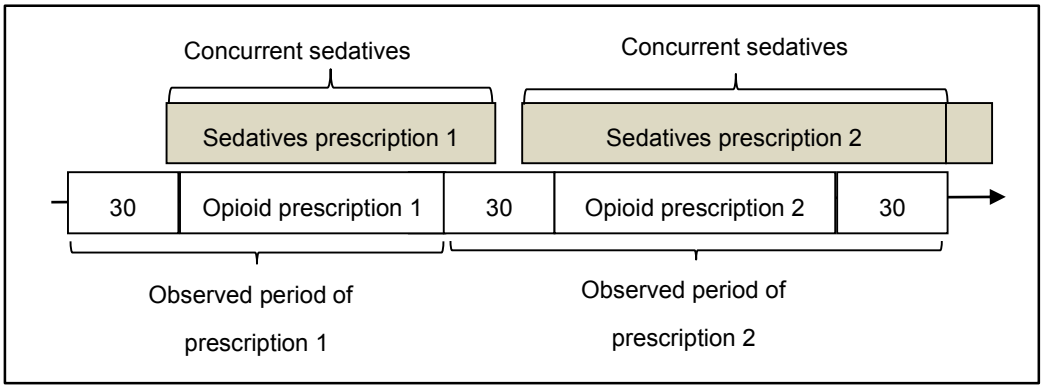
5.3.5. The utilisation of concurrent sedatives for opioid users in each patient-year

For opioid users, sedatives potentially associated with opioid-overdose deaths on published literature including antidepressants, anticonvulsants, antipsychotics, BZDs and z-drugs (zopiclone and zolpidem) were identified by product codes in the CPRD (Appendix 17)[9, 25, 41-44]. According to BNF, antidepressants were categorised into SSRI/SNRI, TCAs and other antidepressants, and anticonvulsants were classified into gabapentin/ pregabalin and other anticonvulsants, and antipsychotics were categorised into first- and second-generation antipsychotics.

The observed period of each opioid prescription was defined as 30 days before each opioid prescription to 30 days after opioid prescription exhausted as the longest duration of potential drug-drug interaction between opioids and sedatives was 30 days from published case reports. If the observed periods of the two consecutive opioid prescriptions overlapped, the end of an observed period of the prior opioid prescription was replaced by the beginning of an observed period of the

next opioid prescription. According to the number of supply days of each sedative prescription, concurrent sedatives were defined as any sedative use overlapped within an observed period (Figure 17).

Figure 17. Definition of an observed period and concurrent sedatives in this study



(Note) *: The end of an observed period of the prior opioid prescription was replaced by the beginning of an observed period of the next opioid prescription, if the observed periods of the two consecutive opioid prescriptions are overlapping.

In each patient-year, the cover rate and the mean daily dose of each category of concurrent sedative during the observed period were calculated for opioid users.

For each sedative prescription, based on the number of supply days, the duration of concurrent use of each sedative prescription was defined as

the duration overlapped within an observed period. For each category of concurrent sedative, the duration of concurrent use of each prescription was summed up on an annual basis to derive the annual duration of concurrent use.

In each patient-year, the observed period for each opioid prescription was summed up to derive annual observed periods. In each patient-year, the cover rate for each category of sedatives was calculated by dividing annual duration of concurrent use by annual observed periods to adjust the difference in observed periods between persistent and non-persistent opioid users.

For each sedative prescription, the quantity was multiplied by the strength (in milligrams) to calculate the dose and then divided by the DDD for each drug[61]. The proportion of supply days with concurrent opioids was calculated by diving the duration of concurrent use by the number of supply days of each sedative prescription. For each sedative prescription, the proportion of supply days which concurrently used with

opioids was multiplied by the total DDD of this prescription to calculate the number of DDD which concurrently used with opioids.

In each patient-year, for each category of sedatives, the number of DDD which concurrently used with opioids was summed up in annual based to derived annual DDD dose which concurrently used with opioids. The annual DDD dose which concurrently used with opioids for each sedative was divided by the annual duration of concurrent use to derive the mean daily dose of concurrent sedatives during overlapped observed period.

5.3.6. Analytical method

In each patient-year, descriptive statistics were used to report the annual trend of the proportion of other opioid users, the annual number of supply days and mean daily dose of other opioids for tramadol users.

For opioid users, the annual trend of the proportion of concurrent sedative users, the cover rate and the mean daily dose of each sedative

category during the overlapping observed period in each patient-year were also presented using descriptive statistics.

The difference in the proportion of other opioid users, annual number of supply days and mean daily dose of other opioids between persistent and non-persistent tramadol users and the difference in the proportion of concurrent sedative users, cover rate and mean daily dose of concurrent sedatives between persistent and non-persistent opioid users in each patient-year were tested by chi-square test and t-test.

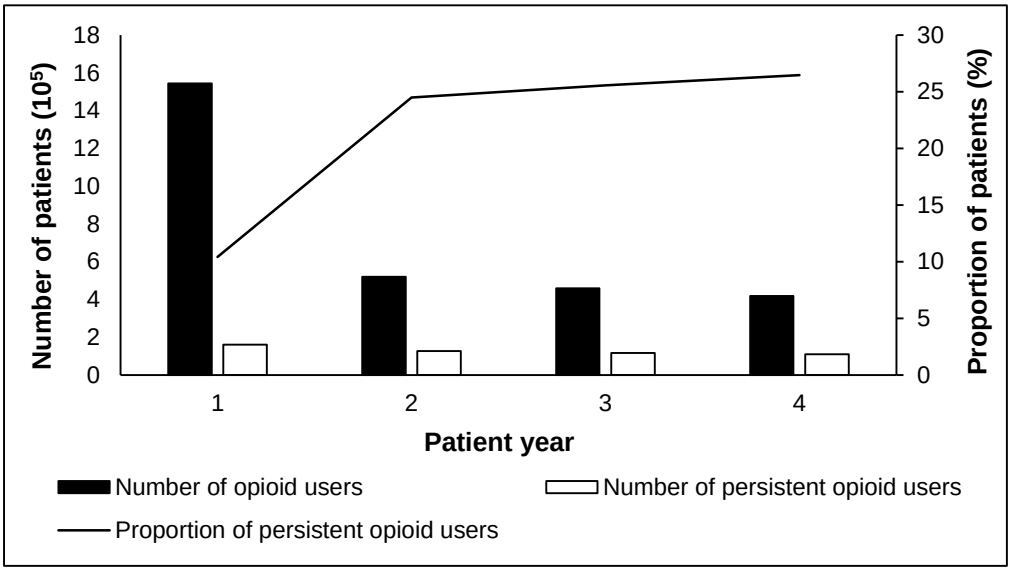
As the trend and the significance of the difference in the utilisation of other opioids for tramadol users and the utilisation of concurrent sedatives for opioid users were similar from the second patient-year onward, this study only presented the results in the first four patient-years.

5.4. Results

5.4.1. Number of persistent opioid users in each patient-year

Overall, 1,749,897 adult patients received an opioid prescription between 2000 and 2015 and 1,544,737 (88.3%) of them who were followed for greater than one year were included in this study. For opioid users followed more than one year, 356,345 (23.1%) patients ever used opioids persistently in at least one of the patient year during the follow-up period, and 160,880 (10.4%) were persistent opioid users in the first patient-year. Once patients received opioid from the second patient-year, about 25% of them would use opioid persistently (Figure 18).

Figure 18. Proportion of persistent opioid users over all opioid users in each patient-year



5.4.2. The utilisation of opioid between persistent tramadol users and non-persistent users in each patient-year

There were 707,868 adult tramadol users between 2000 and 2015 and 621,385 (87.8%) of them were followed for more than one year. Of whom, 164,496 (26.5%) tramadol users ever used tramadol persistently in one of the follow-up patient-year.

Of the 621,385 tramadol users, 466,994 (75.2%) of them ever used other opioids, and the most common opioid been prescribed to tramadol users was short-acting formulations of weak opioids (n=445,791, 71.7%)

followed by long-acting formulations of strong opioids (n=102,769, 16.5%) and short-acting formulations of strong opioids (n=83,264, 13.4%).

In the first patient-year, a higher proportion of persistent tramadol received any type of opioids except short-acting weak opioids when compared to non-persistent tramadol users, but a higher proportion of non-persistent tramadol users were prescribed with any type of opioids when compared to persistent tramadol users from the second patient-year onward (Figure 19).

Persistent tramadol users also had a greater annual number of supply days and mean daily dose for each type of opioid in the first patient-year when compared with non-persistent tramadol users. However, from the second patient-year onward, non-persistent tramadol users had a greater annual number of supply days for all types of opioids except for long-acting strong opioids (Table 15).

Figure 19. Proportion of opioid users in tramadol users in each patient-year

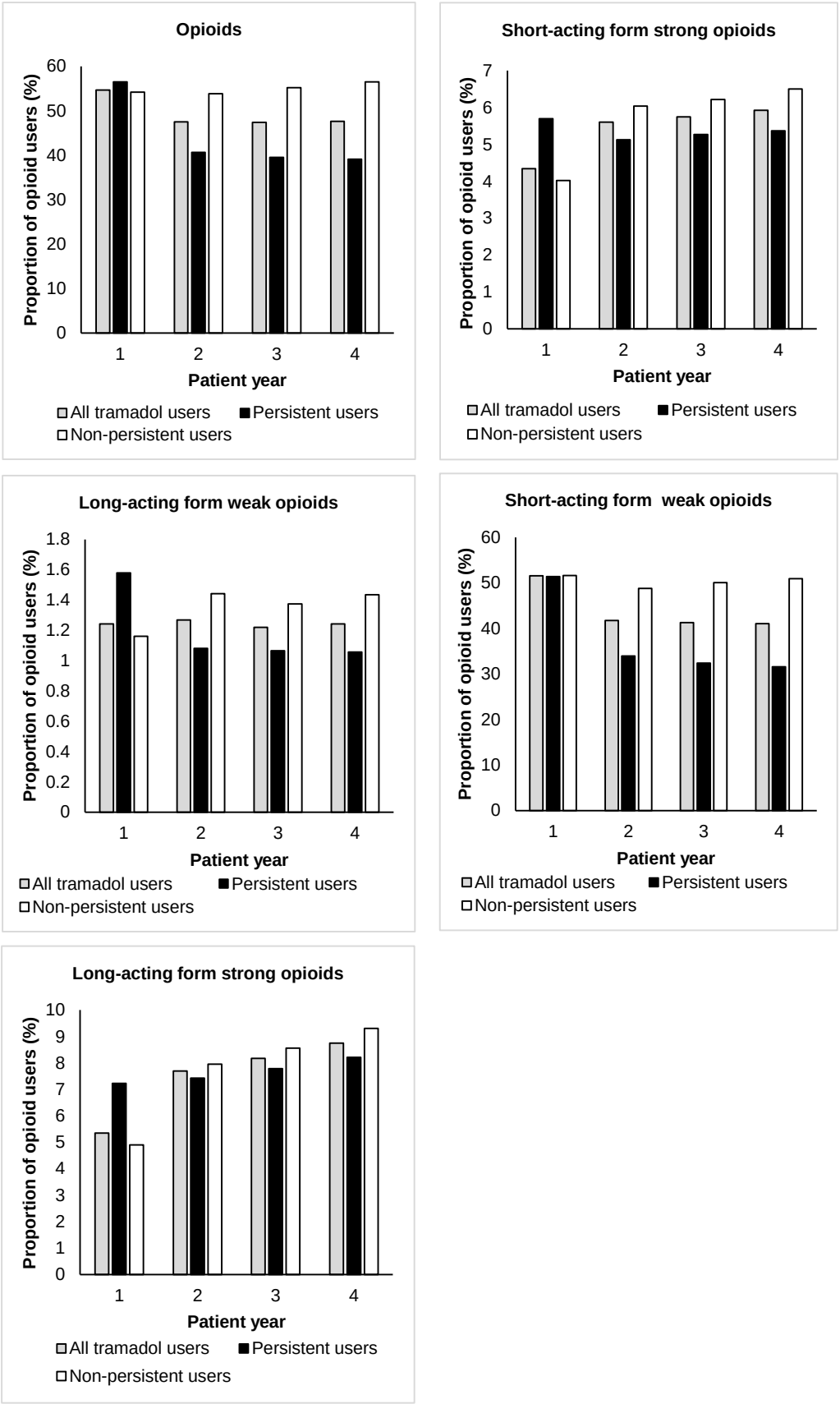


Table 15. Annual number of supply days of other opioids between persistent and non-persistent tramadol users

Opioids and patient year		All tramadol users	Persistent users	Non-persistent users	
		Mean± SD	Mean± SD	Mean± SD	Sig
All opioids	1	48.9±85.8	55.4±91.5	47.3±84.3	*
	2	55.7±95.2	54±98.1	57.3±92.3	*
	3	58.5±99	55.6±101.5	61.4±96.4	*
	4	60.6±101	56.7±103.2	64.7±98.5	*
Short-acting form strong opioids	1	2±16.4	2.8±19.5	1.8±2	*
	2	3±21.1	3.1±22.6	2.9±3	
	3	3.2±22.4	3.3±23.7	3.2±3.2	
	4	3.5±23.7	3.7±25.2	3.3±3.5	*
Long-acting form strong opioids	1	5.9±34.4	7.5±37.8	5.6±33.5	*
	2	9.4±44.5	10±47.6	8.9±41.6	*
	3	10.8±48.6	11.4±51.8	10.1±45.1	*
	4	11.9±51.5	12.6±55.1	11.1±47.4	*
Short-acting form weak opioids	1	41.2±77	45.4±82.6	40.1±41.2	*
	2	43.9±83.8	41.5±86.1	46.1±43.9	*
	3	45.3±86.4	41.7±87.9	48.9±45.3	*
	4	46.2±87.6	41.5±88.4	51.1±46.2	*
Long-acting form weak opioids	1	1.1±14.6	1.3±16.3	1±1.1	*
	2	1.3±17.1	1.4±18.3	1.3±1.3	
	3	1.4±18	1.4±18.9	1.4±1.4	
	4	1.6±19.2	1.5±19.4	1.6±1.6	

(Note) Results are presented in mean and standard deviation; Sig.: Statistically significant difference, i.e. P<0.05

In addition, non-persistent tramadol users had a greater mean daily dose of each type of opioids when compared to persistent tramadol users during the follow-up period except the first patient-year (Table 16).

Table 16. Mean daily OMEQ dose of other opioids between persistent and non-persistent tramadol users in each patient-year

Opioids and patient year		All tramadol users	Persistent users	Non-persistent users	
		Mean± SD	**Mean± SD**	**Mean± SD**	**Sig**
All opioids	1	14±23.5	16.1±27.4	13.5±22.4	*
	2	14.6±30.2	13.3±30.7	15.8±29.7	*
	3	14.9±30.8	13.5±32.4	16.2±29.1	*
	4	15.4±33.3	13.8±33.5	17.1±33	*
Short-acting form strong opioids	1	2.1±13.7	2.7±14.4	2±13.6	*
	2	2.8±15.7	2.5±13.8	3.1±17.3	*
	3	2.8±16.1	2.5±13.2	3.1±18.6	*
	4	2.9±15.2	2.6±14.5	3.2±15.9	*
Long-acting form strong opioids	1	3.7±26.5	5.3±31	3.4±25.3	*
	2	6.1±36.2	5.9±34.3	6.3±37.8	*
	3	6.4±35.8	6.4±36	6.5±35.6	
	4	7.1±40.3	6.8±38.7	7.3±41.9	
Short-acting form weak opioids	1	11±13.5	11.6±13.8	10.9±13.5	*
	2	9.3±13.6	7.8±12.8	10.8±14.1	*
	3	9.3±13.4	7.5±13.1	11.1±13.4	*
	4	9.3±13.3	7.2±12.5	11.4±13.8	*
Long-acting form weak opioids	1	0.33±4.3	0.43±4.4	0.31±4.3	*
	2	0.36±4.2	0.3±3.6	0.41±4.7	*
	3	0.34±3.6	0.3±3.4	0.38±3.7	*
	4	0.35±3.8	0.29±3.2	0.41±4.3	*

(Note) Results are presented in mean and standard deviation; Sig.: Statistically significant difference, i.e. $P<0.05$

5.4.3. The utilisation of concurrent sedatives between persistent opioid users and non-persistent users in each patient-year

During the follow-up period, 812,666 (52.6%) of the 1,544,737 opioid users ever used sedatives concurrently; of which antidepressants were the most common sedatives (37.6%) followed by BZDs (22.7%). Once stratified patients into persistent and non-persistent opioid users, the proportion of concurrent sedative users were significantly higher for persistent opioid users in each patient-year (Figure 20) (Figure 21).

For each category of sedative, significant higher cover rates and mean daily dose of concurrent sedatives were found among persistent opioid users in each patient-year (Table 17) (Table 18).

Figure 20. The proportion of concurrent antidepressants, BZDs and Z-drug users in opioid users in each patient-year

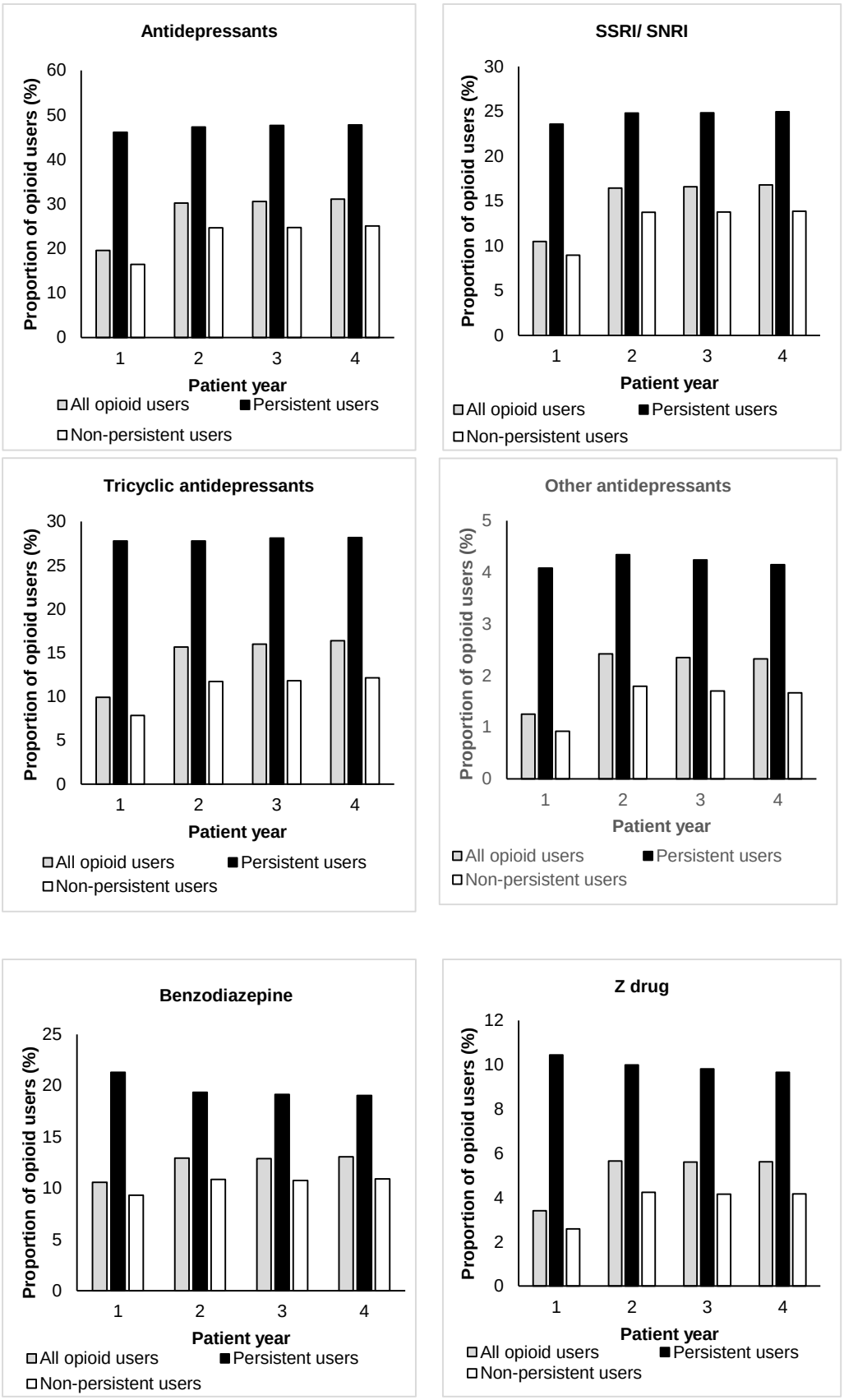


Figure 21. The proportion of concurrent anticonvulsants and antipsychotics users in opioid users in each patient-year

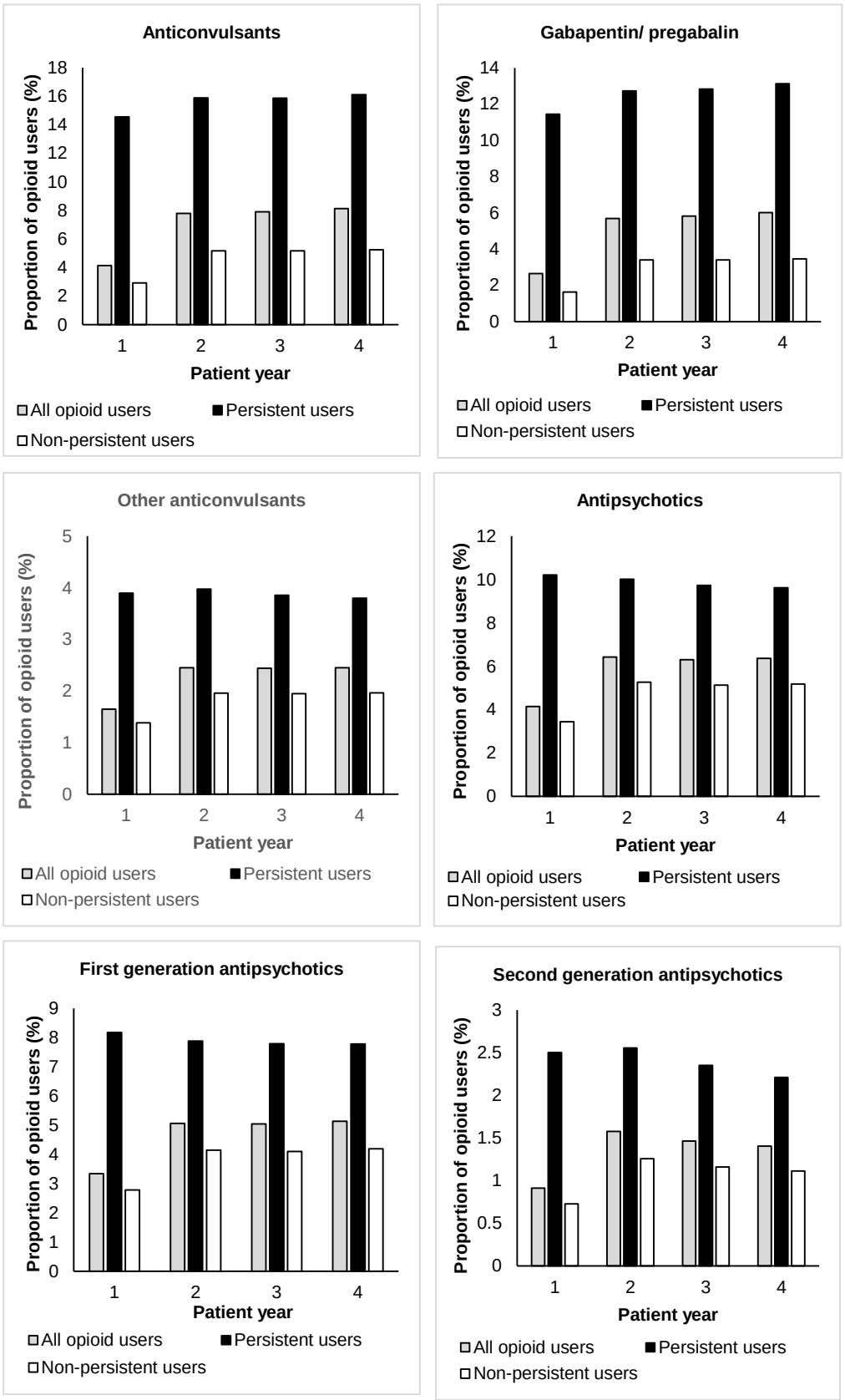


Table 17. The cover rate of sedatives in each patient-year between persistent and non-persistent opioid users

Sedatives and patient year		All opioid users	Persistent users	Non-persistent users	
		Mean± SD	Mean± SD	Mean± SD	Sig
Antidepressants	1	0.13±0.3	0.28±0.38	0.11±0.28	*
	2	0.2±0.35	0.32±0.41	0.16±0.32	*
	3	0.2±0.35	0.33±0.41	0.16±0.32	*
	4	0.21±0.36	0.34±0.41	0.16±0.32	*
Selective serotonin reuptake	1	0.07±0.23	0.14±0.3	0.06±0.22	*
inhibitor/ serotonin norepinephrine	2	0.11±0.27	0.16±0.32	0.09±0.25	*
reuptake inhibitors (SSRI/SNRI)	3	0.11±0.27	0.16±0.32	0.09±0.25	*
	4	0.11±0.28	0.17±0.33	0.09±0.25	*
Tricyclic antidepressants (TCA)	1	0.05±0.19	0.14±0.28	0.04±0.18	*
	2	0.09±0.24	0.16±0.32	0.06±0.21	*
	3	0.09±0.25	0.17±0.33	0.07±0.21	*
	4	0.09±0.25	0.17±0.33	0.07±0.21	*
Other antidepressants	1	0.01±0.07	0.02±0.12	0.01±0.07	*
	2	0.01±0.1	0.02±0.13	0.01±0.09	*
	3	0.01±0.1	0.02±0.13	0.01±0.09	*
	4	0.01±0.1	0.02±0.13	0.01±0.09	*
Benzodiazepine (BZD)	1	0.03±0.15	0.08±0.23	0.03±0.13	*
	2	0.05±0.18	0.09±0.24	0.04±0.16	*
	3	0.05±0.19	0.08±0.24	0.04±0.16	*
	4	0.05±0.19	0.08±0.24	0.04±0.16	*
Z drug	1	0.01±0.1	0.04±0.17	0.01±0.09	*
	2	0.03±0.14	0.05±0.18	0.02±0.12	*
	3	0.03±0.14	0.05±0.18	0.02±0.12	*
	4	0.03±0.14	0.05±0.18	0.02±0.12	*
Anticonvulsants	1	0.03±0.13	0.08±0.23	0.02±0.12	*
	2	0.05±0.19	0.1±0.26	0.03±0.15	*
	3	0.05±0.19	0.1±0.26	0.03±0.15	*
	4	0.05±0.19	0.1±0.26	0.03±0.15	*

(Note) Results are presented in mean and standard deviation; Sig.: Statistically significant difference, i.e. P<0.05, SD: standard deviation

Table 17. The cover rate of sedatives in each patient-year between persistent and non-persistent opioid users (continued)

Sedatives and patient year		All opioid users	Persistent users	Non-persistent users	
		Mean± SD	Mean± SD	Mean± SD	Sig
Gabapentin/ pregabalin	1	0.01±0.1	0.06±0.2	0.01±0.08	*
	2	0.03±0.15	0.07±0.22	0.02±0.11	*
	3	0.03±0.16	0.08±0.23	0.02±0.12	*
	4	0.03±0.16	0.08±0.23	0.02±0.11	*
Other anticonvulsants	1	0.01±0.1	0.02±0.13	0.01±0.09	*
	2	0.02±0.11	0.03±0.14	0.01±0.1	*
	3	0.02±0.11	0.02±0.14	0.01±0.1	*
	4	0.02±0.11	0.02±0.14	0.01±0.1	*
Antipsychotics	1	0.02±0.1	0.03±0.15	0.01±0.09	*
	2	0.02±0.13	0.04±0.16	0.02±0.11	*
	3	0.02±0.13	0.03±0.16	0.02±0.11	*
	4	0.02±0.12	0.03±0.15	0.02±0.11	*
First generation antipsychotics	1	0.01±0.07	0.02±0.1	0.01±0.07	*
	2	0.01±0.09	0.02±0.11	0.01±0.08	*
	3	0.01±0.09	0.02±0.11	0.01±0.08	*
	4	0.01±0.09	0.02±0.11	0.01±0.08	*
Second generation antipsychotics	1	0.01±0.07	0.02±0.11	0.01±0.07	*
	2	0.01±0.1	0.02±0.12	0.01±0.09	*
	3	0.01±0.09	0.02±0.12	0.01±0.08	*
	4	0.01±0.09	0.02±0.11	0.01±0.08	*

(Note) Results are presented in mean and standard deviation; Sig.: Statistically significant difference, i.e. P<0.05, SD: standard deviation

Table 18. The mean daily dose of concurrent sedatives during overlapped observed period in each patient-year between persistent and non-persistent opioid users

Sedatives and patient year		All opioid users	Persistent users	Non-persistent users	
		Mean± SD	Mean± SD	Mean± SD	Sig
Antidepressants	1	0.21±0.69	0.5±0.92	0.18±0.65	*
	2	0.34±0.97	0.55±1.2	0.27±0.86	*
	3	0.35±0.92	0.56±1.1	0.27±0.85	*
	4	0.35±0.86	0.57±1	0.27±0.77	*
Selective serotonin reuptake inhibitor/ serotonin norepinephrine reuptake inhibitors (SSRI/SNRI)	1	0.16±0.72	0.38±1.1	0.14±0.65	*
	2	0.26±1	0.41±1.4	0.21±0.92	*
	3	0.26±0.96	0.42±1.2	0.21±0.84	*
	4	0.27±0.88	0.42±1.1	0.21±0.77	*
Tricyclic antidepressants (TCA)	1	0.05±0.33	0.16±0.56	0.04±0.29	*
	2	0.09±0.46	0.18±0.65	0.06±0.37	*
	3	0.09±0.42	0.18±0.61	0.06±0.32	*
	4	0.1±0.44	0.19±0.61	0.07±0.35	*
Other antidepressants	1	0.02±0.34	0.05±0.35	0.01±0.22	*
	2	0.03±0.36	0.06±0.41	0.02±0.34	*
	3	0.03±0.35	0.06±0.47	0.02±0.29	*
	4	0.03±0.32	0.06±0.41	0.02±0.27	*
Benzodiazepine (BZD)	1	0.11±0.47	0.23±0.67	0.09±0.44	*
	2	0.14±0.5	0.22±0.65	0.11±0.44	*
	3	0.13±0.49	0.21±0.63	0.11±0.43	*
	4	0.14±0.48	0.22±0.63	0.11±0.41	*
Z drug	1	0.04±0.28	0.11±0.39	0.03±0.27	*
	2	0.06±0.3	0.1±0.4	0.04±0.25	*
	3	0.06±0.3	0.1±0.38	0.04±0.26	*
	4	0.06±0.31	0.1±0.39	0.04±0.28	*
Anticonvulsants	1	0.03±0.28	0.12±0.55	0.02±0.23	*
	2	0.06±0.4	0.14±0.54	0.04±0.33	*
	3	0.07±0.4	0.14±0.58	0.04±0.31	*
	4	0.07±0.42	0.14±0.5	0.04±0.38	*

(Note) Results are presented in mean and standard deviation; Sig.: Statistically significant difference, i.e. P<0.05, SD: standard deviation.

Table 18. The mean daily dose of concurrent sedatives during overlapped observed period in each patient-year between persistent and non-persistent opioid users (continued)

Sedatives and patient year		All opioid users	Persistent users	Non-persistent users	
		Mean± SD	Mean± SD	Mean± SD	Sig
Gabapentin/ pregabalin	1	0.02±0.21	0.1±0.44	0.01±0.16	*
	2	0.05±0.36	0.12±0.5	0.03±0.29	*
	3	0.05±0.37	0.12±0.58	0.03±0.25	*
	4	0.05±0.38	0.12±0.48	0.03±0.33	*
Other anticonvulsants	1	0.01±0.22	0.03±0.37	0.01±0.19	*
	2	0.02±0.21	0.03±0.27	0.01±0.18	*
	3	0.02±0.21	0.02±0.19	0.01±0.22	*
	4	0.02±0.2	0.02±0.2	0.01±0.2	*
Antipsychotics	1	0.02±0.38	0.04±0.22	0.01±0.39	*
	2	0.02±0.2	0.04±0.25	0.02±0.17	*
	3	0.02±0.22	0.04±0.23	0.02±0.22	*
	4	0.02±0.21	0.03±0.22	0.02±0.2	*
First generation antipsychotics	1	0.01±0.36	0.02±0.17	0.01±0.37	*
	2	0.01±0.2	0.02±0.18	0.01±0.2	*
	3	0.01±0.25	0.02±0.18	0.01±0.27	*
	4	0.01±0.21	0.02±0.23	0.01±0.2	*
Second generation antipsychotics	1	0.01±0.14	0.02±0.18	0.01±0.14	*
	2	0.01±0.17	0.02±0.21	0.01±0.15	*
	3	0.01±0.19	0.02±0.18	0.01±0.19	*
	4	0.01±0.17	0.02±0.18	0.01±0.17	*

(Note) Results are presented in mean and standard deviation; Sig.: Statistically significant difference, i.e. P<0.05, SD: standard deviation.

5.5. Discussion

5.5.1. Main findings

The use of a MDA is feasible to identify persistent opioid users in the UK primary care settings. Over three-quarter of tramadol users received other opioids during the follow-up period, and a higher proportion of non-persistent tramadol received other opioids and had a greater annual number of supply days and mean daily opioid dose from the second patient-year onward. As opioids shared a common mechanism to cause serious adverse events, opioids should be treated as a class to evaluate their safety.

More than half of opioid users used sedatives concurrently with opioids during the follow-up period, and antidepressants were the most common sedatives followed by BZDs. Compared to non-persistent opioid users, a higher proportion of persistent opioid users were concurrently prescribed with sedatives due to longer observed periods related to persistent opioid prescribed. Moreover, higher mean daily dose and cover rate were also found among persistent opioid users in each patient-year after adjusting the difference in observed periods between persistent and

non-persistent opioid users.

5.5.2. Non-persistent tramadol users had higher utilisation of other opioids when compared to persistent tramadol users

This study found non-persistent tramadol users were prescribed other opioids for longer duration and higher mean daily dose than persistent users, which implied serious adverse events might involve other opioids. In fact, about 20% of tramadol-related deaths also involved heroin/morphine in 2013 in England and Wales[25]. More than half of opioid overdose deaths in North Carolina in 2010 involved more than one opioid[226] and about 35% of opioid-related deaths in the UK in 2013 involving heroin/morphine combined several opioids [25]. As opioids have similar mechanisms to cause serious opioid-related adverse events, such as respiratory depression, all opioids need to be considered when evaluating the association between opioid utilisation and opioid-related adverse events.

A detailed case report of opioid-related deaths can help to understand

the key determinants and develop the hypothesis of its association with the utilisation of prescribed opioids. However, information about opioid-related deaths published by the UK ONS was based on the reports from coroners, and the lack of reporting a history of prescribed medications has also been mentioned[227]. Currently, there was no research exploring the utilisation of prescribing opioid for opioid-related deaths in the UK and the association between opioid-related deaths and utilisation of prescribing opioids remains unclear.

5.5.3. The potential reasons for higher utilisation of concurrent sedatives among persistent opioid users

Comparing to the non-persistent opioid users, a higher proportion of persistent opioid users were prescribed sedatives concurrently. After adjusting the duration of opioid prescribing period by calculating the cover rate, a higher cover rate was also found among persistent opioid users in each patient-year. Those findings are consistent with previous publications which measured concomitant sedatives and found a higher proportion of persistent opioid users or chronic opioid users were prescribed sedatives, such as BZDs or antidepressants[43, 103].

Several reasons could partly explain the higher cover rate and mean daily dose of concurrent sedatives among persistent opioid users. Firstly, in addition to pain relief, improving sleep, emotional health and quality of life are secondary treatment goals for patients with chronic pain, and a combination of treatments maybe necessary[11, 12, 228]. Several psychological conditions, such as depression and sleep disorders have been found to be associated with persistent opioid utilisation[2, 208, 210, 217-219], and hence it is expected that persistent opioid users would concurrently be prescribed with these sedatives. In addition, several antidepressants are indicated for neuropathic pain in the UK, and hence the combination of antidepressants might be prescribed for pain relief[229].

Finally, the combination of opioids and BZDs has been identified as an indicator of addiction in a cross-sectional questionnaire survey, and a cohort study applying prescribing data also used the combination of high dose opioid and BZD as an indicator of problematic opioid use[220, 230]. As a close link between persistent opioid utilisation and problematic opioid use has been identified[6], a higher proportion of persistent opioid users who combine BZD was unsurprising. However, as persistent opioid

users were more likely to have the common psychological illness and substance misuse disorders, further studies evaluating the safety of persistent opioid utilisation should consider the effects of those comorbidities and co-medications.

5.5.4. The higher proportion of persistent opioid users prescribed antidepressants might be related to the increased prescribing

Mellbye *et al.* (2012) also applied a MDA to define persistent opioid utilisation for patients initiated an opioid in 2008 in Norway and described the prevalence of concomitant sedatives among persistent opioid users in the first patient-year[103, 224]. Compared to this study that measured concurrent sedatives, Mellbye *et al.* defined any sedative prescribed during the year as concomitant medications, and hence a higher proportion of persistent opioid users concomitantly used BZD (53%) in the first patient-year when compared to the results from this study (21.3%)[103].

However, a higher proportion of persistent opioid users were concurrently prescribed antidepressants (46.1%) in the UK general practice when compared with the results (40%) from the study conducted by Mellbye *et al*[103]. Compared to BZD with a relatively constant annual number of prescriptions between 2008 and 2012[231], the annual number of prescriptions of antidepressants has more than doubled from 2006 to 2016 and has become the therapeutic category with the greatest rise in all BNF categories in England[232].

The potential reason of the higher proportion of persistent opioid users concurrently prescribed antidepressants in this study might be because Mellbye *et al.* only applied prescribing data in 2008, but this study used prescribing data up to 2015. Therefore, the increased trend of antidepressants prescribing in the UK might lead to the higher proportion of persistent opioid users concurrently been prescribed antidepressants in this study when comparing to studies from other countries.

Higher risk of opioid-related deaths was found among patients

concurrently prescribed opioids and BZDs, and it is recommended to avoid the combination in the UK[5, 9, 25, 41-44]. However, the association between opioid-related harm and antidepressants is still controversial as antidepressants may increase the risk of oversedation but also help to control patients with depression from suicide. Currently, there is no pharmacoepidemiological study evaluating the association between opioid-related deaths and concurrent antidepressants among opioid users in the UK.

5.5.5. Strengths and limitations

Comparing to the published study only applying data from Scotland[233], this is the first longitudinal study to explore concurrent sedative prescribing to opioid users using prescribing records from the UK primary care setting. Comparing with the previous study that applied the definition of 'concomitant medication' to measure medication as indicators of patients' comorbidity or disease severity, the definition of 'concurrent medication' used in this study was more suitable to identify potential drug-drug interaction for further safety evaluation[224].

However, some limitations to this study need to be acknowledged. First, the results from Chapter 3showed that the number of active patients registered in the CPRD decreased from 2010 (Appendix 5) and hence the prevalence of concurrent sedative users might be an underestimate as the number of opioid users decreased. In addition, from the second patient-year onward, it is possible that non-persistent users had a history of persistent utilisation in previous patient-years, but this study did not consider the potential influence of earlier patient-years. Furthermore, persistent opioid utilisation is related to common psychological conditions, and it is possible that higher utilisation of concurrent sedatives among persistent opioid users is related to higher prevalence of psychological illnesses. However, prescribing records in the CPRD cannot link to specific indications, and hence it is hard to link prescriptions with particular disease conditions.

5.6. Conclusion

Non-persistent tramadol users received other opioids with longer duration and higher mean daily dose. Therefore, further studies need to evaluate the safety of opioid class rather than a single opioid. Compared

to non-persistent opioid users, persistent opioid users were more likely to be concurrently prescribed sedatives, and higher mean daily dose and cover rate were also found among persistent opioid users even adjusting the difference in observed periods. In order to evaluate the association between opioid utilisation and opioid-related deaths, further studies need to adjust the influence of concurrent sedatives.

Chapter 6. Identification of opioid-related deaths and tramadol-associated serious harms from the United Kingdom primary care database

6.1. Introduction

The number of opioid-related deaths in 2016 increased by 63% when compared to the number in 2012 in the UK[234]. The results in Chapter 5 showed that more than 75% of tramadol users received other opioids during the follow-up period and non-persistent tramadol users received other opioids with a greater annual number of supply days and mean daily dose when compared to persistent tramadol users (Section 5.4.2, Page 165).

As the majority of opioid-induced adverse events are dose-dependent and associated with the dose of all opioids rather than single opioid[7, 9], opioids should be treated as a class to evaluate its association with opioid-induced adverse events. However, there was no research evaluating the association between opioid-related deaths and prescribed opioids in the UK.

Although the number of opioid-related deaths involving tramadol has decreased since classified tramadol as a controlled drug in England and Wales from June 2014[234], other tramadol-related serious adverse events may occur due to pharmacokinetic and pharmacodynamic interactions with antidepressants[31]. The concurrent use of tramadol and antidepressants which also reduce neuronal serotonin reuptake has been found associated with serious adverse events [235, 236].

Slow metabolizers of tramadol and the concomitant using CYP2D6 inhibitors[237], such as paroxetine, fluoxetine and duloxetine, reduce the clearance of tramadol and hence drug-drug intervention causes serious adverse events including seizures, serotonin syndrome, hypoglycaemia[164] and hyponatremia[165]. Higher tramadol dose for persistent tramadol users have been presented in the previous chapter (Section 3.4.2, Page 94) and increasing annual opioid dose was also associated with increasing use of concomitant antidepressants[104]. However, in the UK, all studies evaluate the association between serious adverse events such as seizures[168, 169], hypoglycaemia[167] and hyponatremia[166] and tramadol utilisation within 90 days after tramadol

initiation rather than an extended period. Currently, the long-term incidence of serious tramadol-related adverse events and their association with long-term tramadol utilisation remain unclear.

Comparing to the evidence from RCTs that only considers clinical efficacy as primary outcome and inconsistently reports adverse events despite the recommendations from Consolidated Standards of Reporting Trials (CONSORT) statement[238, 239], rare adverse events are more likely to be detected in Phase IV post-marketing surveillance studies which include a larger population from real-world practices when compared to clinical trials that follow patients for a short period of time and include restricted population[240, 241]. For long-term and suspected rare adverse events, epidemiological studies such as case-control studies were recommended to identify the association between adverse events and medication by applying post-marketing data such as primary care databases[241].

In the UK, over 98% of residents are registered with a general practice,

and longitudinal clinical records were prospectively collected from practitioners' daily records[242]. Primary care databases, such as CPRD, THIN and Q Research provide longitudinal data, and hence could be used to assess the association between long-term exposure and rare adverse events. As the largest verified longitudinal primary care database in the UK, use of CPRD and linkage data for the investigation of rare adverse events has increased recently[214-216]. In addition, for serious adverse events which result in admission to hospital, linkage data with primary care databases such as the linkage of HES, ONS mortality data and CPRD provide additional information allowing the diseases which are managed and confirmed in the secondary care being identified[242, 243].

However, the original purpose of healthcare databases was for a claim or collecting information for routine clinical practice rather than research. Applying inappropriate data sources and methods to identify adverse events may lead to misestimating of the association between medication use and adverse events and has been recognised in previous publications.

There are two concerns about data sources from published literature evaluating the safety of tramadol and opioids in the UK, including database selection and the generalisability of data sources. Firstly, without applying linkage data, such as HES to identify serious adverse events needing hospital admission caused underestimation of seizure among tramadol users in the UK primary care. Gasse *et al.* (2000) have evaluated the incidence of seizure for tramadol users by applying Read code in the CPRD between November 1996 and August 1998, but only 21 cases of seizure were identified[168]. Published studies have used HES to identify seizure for patients with depression[244, 245], but there was no research using HES to evaluate the association between tramadol utilisation and seizure in the UK even though tramadol was launched in the UK in 1993.

Secondly, regarding the generalisability of data sources, each primary care database in the UK only covered a proportion of residents from particular geographic regions and was not necessarily eligible to link to other data sources, such as CPRD including 8% of general population and only information of registrants from practices in parts of England and

Wales (about 60%) can be linked to HES and ONS mortality data[186, 188]. The CPRD population is demographically representative of the UK general population[187, 188], but it is still unclear whether opioid-related death identified from sampling data sources, such as CPRD and linkage ONS mortality data was representative to the total opioid-related deaths in the UK.

Regarding the feasibility of applying methods to identify opioid-related death and tramadol-related adverse events, such as serotonin syndrome, there are also two concerns including the feasibility of applying modified methods to identify opioid-related deaths and the completeness of diagnosis.

Firstly, although the ONS published method to define drug-misuse death and substance involving in the causes of death (as opioid-related death was defined as a subset of drug-misuse deaths where an opioid was mentioned on the death certificate[23, 24]), the published method included all opioids and hence methadone-related deaths cannot be differentiated

once applied the method from ONS[28]. However, in the UK, methadone was mainly indicated for substitution therapy with daily dispensing and supervision of methadone dosing[28, 135, 225]. Therefore, methadone-related deaths in the UK were mainly associated with the implementation of opioid substitute treatment rather than prescribed opioids[25, 28, 135]. Although ICD codes have been applied to identify opioid-overdose deaths among drug-overdose deaths in the US[7, 9, 41, 246], those ICD codes were applied to describe death due to opioid poison rather than other reasons such as opioid abuse. According to the definition from ONS[23, 24], as opioid-related deaths were not necessarily caused by opioid poison in the UK, the feasibility to apply those ICD codes to identify opioid-related deaths among drug-misuse deaths was still unclear.

Secondly, the completeness of clinical diagnosis would be a potential concern when using health care database to identify adverse events as misclassification and underreporting of events would lead to bias estimates of association in epidemiology studies[242, 243, 247]. Due to the variation in clinical presentation, lack of awareness due to rare incidents

and the lack of specific diagnosis codes in clinical classification systems, serotonin syndrome might be under-diagnosed and under-recorded in clinical practice system. Serotonin syndrome is a composite of several non-specific symptoms including tremor and fever[248]. The improved Hunter Serotonin Toxicity Criteria are more sensitive and specific than previous diagnosis criteria[248], but the clinical presentation and severity varied widely among patients, and the diagnosis still relies on physicians' subjective judgement as an objective diagnostic test was lacking[248]. Consequently, the diverse manifestations of serotonin syndrome might lead to under-diagnosis[249, 250]. In addition, there was currently no specific diagnosis code for serotonin syndrome in current clinical classification systems, such as ICD and hence under-record of serotonin syndrome was expected[251].

To evaluate the association between serious adverse events among tramadol users and opioid-related deaths for opioids users, it is crucial to explore the feasibility of applying healthcare database and methods of adverse events identification.

6.2. Aim and objectives

This chapter aimed to explore the feasibility of applying linkage datasets and published methods to define opioid-related deaths for opioid users and serious adverse events in tramadol users in UK primary care data with the linkage of HES and ONS death certificate for further safety evaluation of persistent opioid and tramadol utilisation. The objectives of this chapter included:

(1) To identify opioid-related deaths in linkage dataset and describe the trend of opioid-related deaths across the calendar year for opioid users

(2) To identify adverse events potentially related to tramadol in linkage dataset for tramadol users

(3) To describe the long-term incidence rate and time-to events of serious adverse events potentially related to tramadol

6.3. Methods

6.3.1. Study design and data source

This retrospective cohort study used three data sources, including CPRD from 1987 to 2015 linked with HES from 1990 to 2012 and ONS death certification from 1998 to 2015 to ensure the identification of serious adverse events from HES/ONS death certification related to opioid prescriptions in CPRD.

The summary of CPRD was listed in chapter 4 (Section 4.3.1, Page116). The HES is a claim-based dataset which included information about hospital admissions, outpatient appointments and accident and emergency attendances at NHS hospitals in England from 1989, 2003 and 2007 onwards. Patients' demography data, administrative information and clinical information are collected with a standard specification form, and clinical information such as diagnoses and procedure was coded by the ICD-10 diagnosis codes and the Office of Population Censuses and Surveys classification of interventions and procedures-version 4. Patients treated in both NHS funded hospitals in England and private treatment centres were contained in HES and more

than 12 million new admission records being added for each British government fiscal year. For each hospitalisation, there are one or more episodes referring to a period within a hospitalisation when the patient was treated under a particular consultation, and up to 20 diagnoses could be found for each episode.

According to the Births and Deaths Registration Act (1836), the ONS death certification is a registry including all deaths occurring in England and Wales from 1998, and any death in the UK should be registered within five days from the date of death on the Registration Online system (RON). In addition, the cause of death should be recorded by a medical practitioner with ICD-10 codes when the death is certified. Validation checks are performed to ensure the information is correct when data were entered into RON, and regular diagnostic tests were performed by the ONS to identify potential inconsistencies. Therefore, the ONS death certification should provide comprehensive and validated records for this study. The study protocol was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (Protocol number: 12_007RA).

6.3.2. Data management and extraction

In order to identify events among different patient groups, all adult opioid users were included in the measurement of overall mortality, and two additional subcohorts were selected from all opioid users. Adult opioid users with linkage eligibility to ONS mortality certificate were selected from all adult opioid users and included to identify drug-misuse deaths and opioid-related deaths. Adult tramadol users who were eligible to link the CPRD data with HES data were also selected from all opioid users and included to identify serious adverse events (Figure 22).

The procedures to identify opioid (Figure 22) and tramadol users (Figure 23) and extract relevant data were mentioned in the following process. First, prescription records of opioid preparations listed in the BNF were identified from product dictionary inbuilt in the “product browser” on the CPRD GOLD online system (Appendix 14 and Appendix 15). Second, a list of codes representing patients who were prescribed those opioid prescriptions was generated by applying the product codes in the “define tool”. Prescription records before the ‘up-to-standard practice date’, which is an indicator of irregularities in practices according to mortality

rate and continuity in data recording within the practices, were excluded.

Third, the identified patients' linkage eligibility to HES and ONS mortality data was checked by matching the list of patient codes (previously generated by the "define tool") with the 'source file' which was provided by a trusted third party[243], that included all patients who registered in English practices which consented to take part in the linkage process to HES and ONS mortality data.

Finally, all patients' records in the relevant files (i.e. patient and therapy files) of CPRD were extracted via the "extraction tool" in CPRD GOLD. For opioid users who were eligible to link the CPRD data with ONS mortality data, the date of death and the cause of death were extracted. For tramadol users who were eligible to link CPRD with the HES data, the date of diagnosis and diagnosis codes from hospitalisation and episode file were extracted.

Figure 22. Data extraction and analytical framework for opioid users

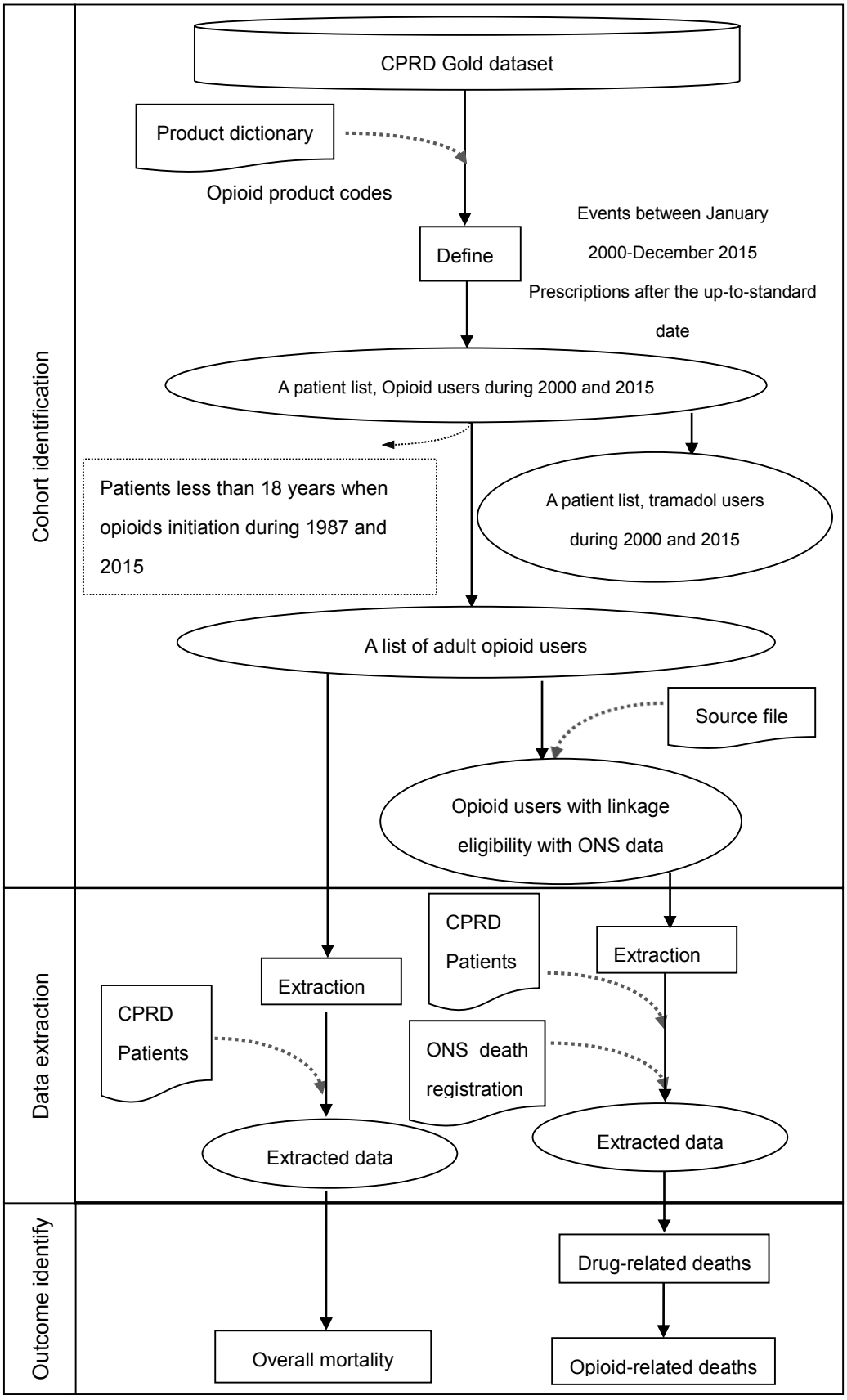
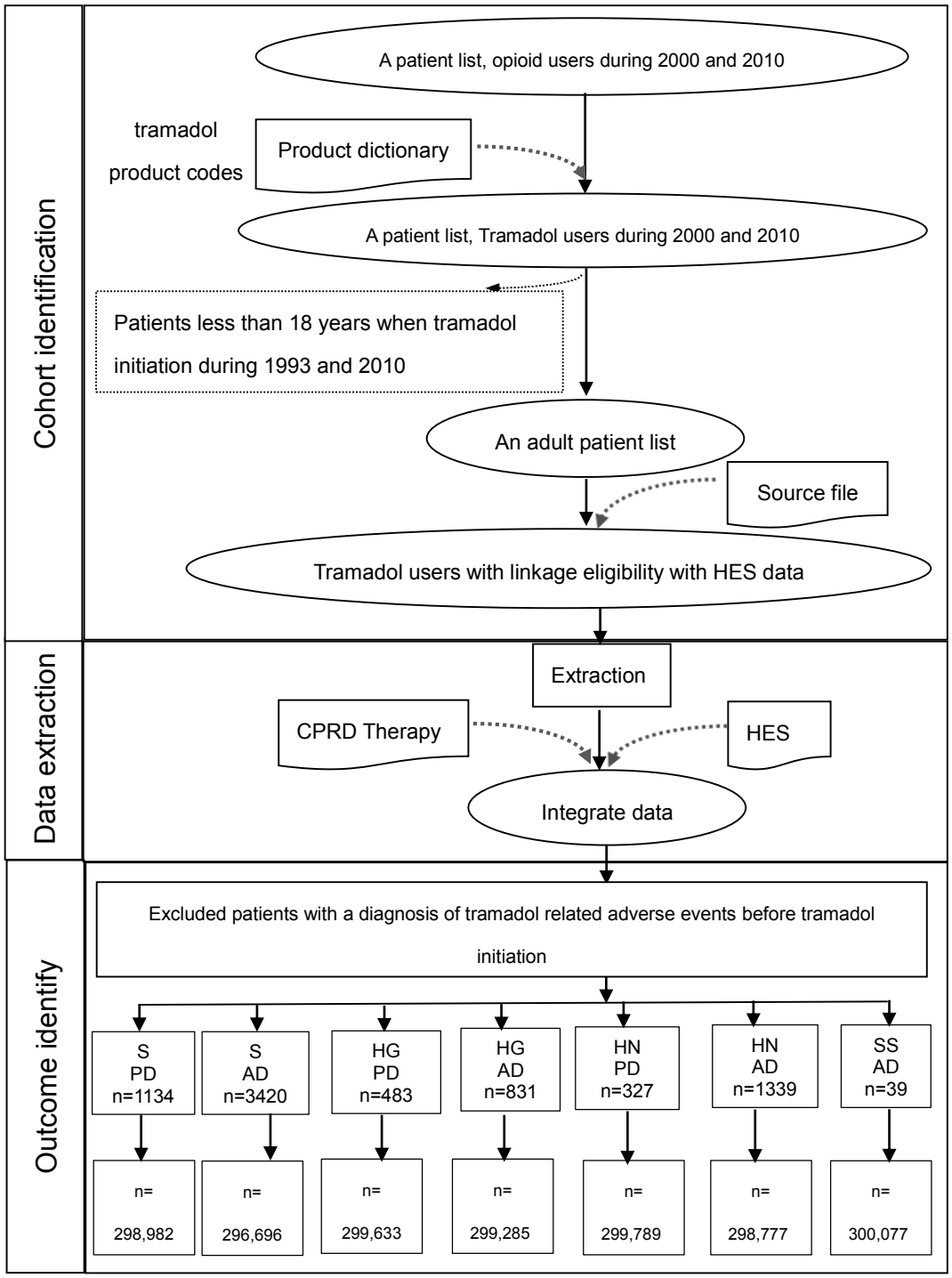


Figure 23. The process of data extraction and integration and analytical framework for tramadol users

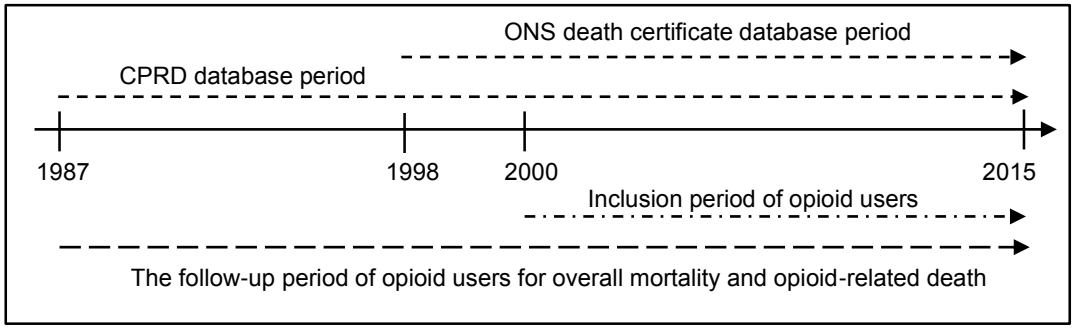


(Note) PD: primary diagnosis in an episode of hospitalisation, AD: all diagnosis in an episode of hospitalisation, SS; serotonin syndrome, HES: Hospitalisation episodes, S: seizure, HG: Hypoglycemia, HN:Hyponatremia

6.3.3. Study cohort

To investigate the occurrence of all-cause mortality related to opioid users, adult opioid users were defined as CPRD registrants who were prescribed with oral and transdermal opioid formulations between January 2000 and December 2015 and aged more than 18 years on the index date (the date of first opioid prescriptions between January 1987 and December 2015). Among adult opioid users, patients with linkage eligibility to ONS mortality certificate were identified by checking linkage eligibility in the source file provided from CPRD (Figure 22). All adult opioid users and the subcohort were both followed from the index date to death, the end of registration, the date of drug-misuse death identified from ONS death certificate and December 2015, whichever comes first. The time periods of data sources, opioid users inclusion and follow-up were summarised in Figure 24.

Figure 24. Time periods of data sources, opioid user inclusion and follow-up for adult opioid users

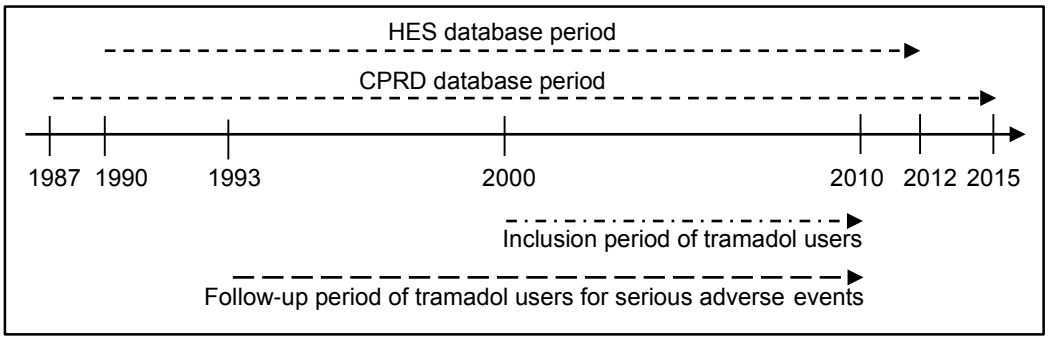


To investigate serious adverse events, a subcohort of adult tramadol users, i.e. adult CPRD registrants (age >18 years on the index date, the date of first tramadol prescription between January 1993 to December 2010) who were prescribed oral tramadol formulations between January 2000 and December 2010 were selected from opioid users by product codes of tramadol from the CPRD product dictionary.

Adult tramadol users who were ineligible to link CPRD data with HES data were excluded. In each outcome measure of tramadol-related adverse events, tramadol users with recorded of tramadol-related adverse events before the index date were excluded in that part of analysis (Figure 23).

Adult tramadol users who were eligible to link the CPRD data with HES data were followed from the index date to tramadol-related adverse events, death, the end of registration and December 2010, whichever comes first. The time periods of data source, tramadol users' inclusion and follow-up were summarised in Figure 25.

Figure 25. Time periods of data sources, tramadol user inclusion and follow-up for adult tramadol users



6.3.4. Outcome measures

The original definition of drug-misuse death from the UK ONS was applied to identify drug-misuse death in ONS death certificate[23, 24]. The definitions used in published pharmacoepidemiology studies or government guidance to identify deaths related to different opiates, such as methadone and prescribing opioids were adapted to develop clinical and operational definitions (the approach to identify events in the

database) were adopted to identify opioid-related death from ONS death certificate (Table 19)[7, 9, 43].

In addition, opioid-related death identified from ONS death certificate were further categorised into all opioid-related death, non-methadone opioid-related death, non-heroin opioid-related death and neither-methadone nor heroin opioid-related death. Those definitions partially overlapped and were applied to differentiate the change in the number of opioid-related deaths involving different opioids (increasing methadone-related deaths in the UK from 2010 due to the more limited availability of heroin) in order to check the feasibility of applying ONS death certificate to define opioid-related deaths.

Adult tramadol users with linkage eligibility to HES were included in the measurement of serious adverse events (Figure 23). Serious adverse events in tramadol users included seizure, hospitalisation for hypoglycaemia, hospitalisation for hyponatremia and serotonin syndrome. According to the definitions from published

pharmacoepidemiology studies and diagnosed criteria, clinical and operational definitions were developed to identify serious adverse events in HES data in tramadol users (Table 20)[166, 167, 244, 245, 248].

To explore how events were recorded in HES, primary diagnosis and any diagnosis (up to 20 diagnoses in one hospitalisation episode) for each episode of hospitalisation were used as information sources to identify seizure, serotonin syndrome and hospitalisation for hypoglycaemia and hyponatremia. Relevant ICD-10 diagnosis codes related to identifying drug-misuse death and tramadol-related adverse events were listed in Appendix 6, Appendix 7 and Appendix 8. According to published literature[249, 252, 253], serotonergic agents were identified, and the product codes were listed in Appendix 18.

6.3.5. Data analysis

In order to identify the frequency of individual outcome measures among each study cohort, the number of patients diagnosed with individual outcome measure during the follow-up period and the incidence rate for

each outcome measures were descriptively reported for each cohort. The incidence rate of each outcome measure was calculated by dividing the number of new events by follow-up duration among included patients who were measured in patient-year and multiply by 10000 to derive the number of events per 10000 patient-years.

In order to benchmark the results identified from the linkage ONS death certificate with national statistics, the number of each category of opioid-related death identified from ONS death certificate in each calendar year from 2000 to 2015 were reported graphically.

In order to describe the correlation between time and the occurrence of outcome measures, the follow-up period from opioid initiation to the date of first events was defined as time-to-event and presented by survival curve for patients with a record of each outcome measure. The time-to-event was summed up and divided by the number of events to calculate the mean time-to-event for each outcome measure.

Table 19. Definition of overall mortality and death-misuse deaths

	Clinical definition	Data source	Operational definition
Overall mortality	All of the deaths that occurred, regardless of the cause.	CPRD	A record of transfer out of original practice due to death in patient data in the CPRD.
Drug-misuse deaths	Death happens when the cause of death recorded on the death certificate is drug poisoning, drug abuse or drug dependence.	ONS	One of the ICD-10 diagnosis codes related to drug-misuse deaths in any cause of death in ONS death registration.
Opioid-related deaths	Death happens when the cause of death recorded on the death certificate is drug poisoning, drug abuse or drug dependence and opium was involved	ONS	One of the ICD-10 diagnosis codes related to drug-misuse deaths in any cause of death in ONS death registration in combination with a T-code indicated any opioid.
Non-methadone opioid-related deaths	Death happens when the cause of death recorded on the death certificate is drug poisoning, drug abuse or drug dependence which involved opium but not included methadone	ONS	One of the ICD-10 diagnosis codes related to drug-misuse deaths in any cause of death in ONS death registration in combination with a T-code indicated any opioid but not included methadone (T40.3).
Non-heroin opioid-related deaths	Death happens when the cause of death recorded on the death certificate is drug poisoning, drug abuse or drug dependence which involved opium but not included heroin	ONS	One of the ICD-10 diagnosis codes related to drug-misuse deaths in any cause of death in ONS death registration in combination with a T-code indicated any opioid but not included heroin (T40.1).
Neither- methadone nor heroin opioid-related death	Death happens when the cause of death recorded on the death certificate is drug poisoning, drug abuse or drug dependence which involved opium but not included heroin and methadone	ONS	One of the ICD-10 diagnosis codes related to drug-misuse deaths in any cause of death in ONS death registration in combination with a T-code indicated any opioid but not included heroin and methadone (T40.1 and T40.3).

(Note) CPRD: Clinical Practice Research Datalink, ONS: Office for National Statistics, ICD-10: International Classification of Diseases, 10th Revision
Relevant ICD-10 diagnosis codes were listed at

Table 20. Definition of tramadol-related outcome measure

	Clinical definition	Information source	Operational definition
Seizure	A seizure is the manifestation of an abnormal, hypersynchronous discharge of a population of cortical neurons.	HES HES	One of the ICD-10 diagnosis codes in the primary diagnosis of hospitalisation One of the ICD-10 diagnosis codes in any diagnosis of hospitalisation
Hospitalisation for hypoglycaemia	Blood glucose level less than 70 mg/dL and need hospitalisation	HES	One of the ICD-10 diagnosis codes in the primary diagnosis of hospitalisation One of the ICD-10 diagnosis codes in any diagnosis of hospitalisation
Hospitalisation for hyponatremia	A serum sodium concentration <135 mmol/L and need hospitalisation	HES	One of the ICD-10 diagnosis codes in the primary diagnosis of hospitalisation One of the ICD-10 diagnosis codes in any diagnosis of hospitalisation
Serotonin syndrome	Hunter serotonin toxicity criteria: serotonin toxicity is positive if 1 of the four following criteria was met and patients took serotonergic agents 1. Spontaneous clonus 2. Inducible clonus/ ocular clonus + agitation/ diaphoresis 3. Inducible clonus/ ocular clonus + hypertonia + body temperature >38 °C 4. Tremor + hyperreflexia	HES and CPRD	One of the following criteria identified by ICD-10 in any diagnosis of hospitalisation and a record of prescription of serotonergic agents in therapy file of CPRD in 30 days before hospitalisation 1. Clonus 2. Ocular clonus + agitation 3. Ocular clonus + diaphoresis 4. Ocular clonus+ hypertonia + body temperature >38 °C 5. Tremor + hyperreflexia 6. Tremor + hyperreflexia/hypertonia

(Note) CPRD: Clinical Practice Research Datalink, HES: Hospital Episode Statistics, ICD-10: International Classification of Diseases, 10th Revision
Relevant ICD-10 diagnosis codes were listed at

6.4. Results

6.4.1. Selection of study cohort

Overall, 1,794,654 patients prescribed with an oral and transdermal formulation of opioids between January 2000 and December 2015, of whom 1,749,897 were adult opioid users and 1,021,885 (58.4%) of the adult opioid users had complete data with linkage eligible to the ONS death certification.

There were 526,624 patients prescribed oral tramadol prescriptions between January 2000 and December 2010 and 524,587 of them were more than 18 years when tramadol was initiated. Of the 524,587 adult tramadol users, 300,116 (57.2%) were linkage eligible to the HES data. After excluding patients with diagnosed records of interested events before the index date, the number of patients included in the analysis of each tramadol-related adverse event was presented in Figure 23.

6.4.2. All-cause mortality and drug-misuse deaths for opioid users

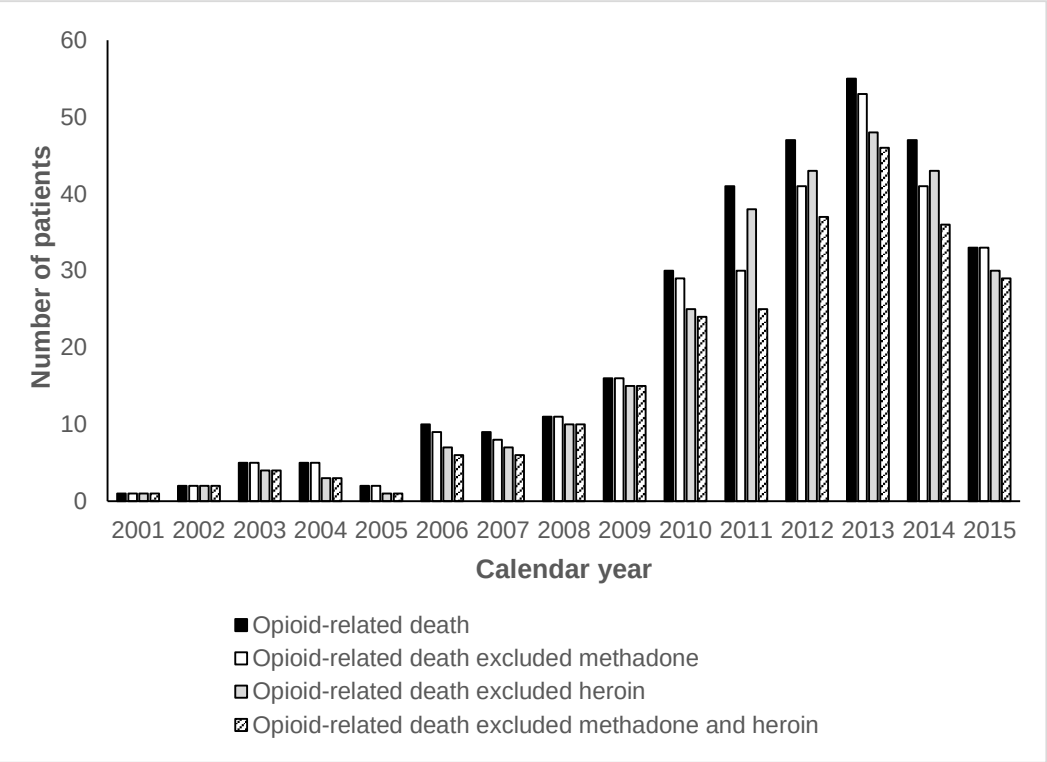
For the 1,749,897 adult opioid users in UK primary cares, the mean follow-up duration from opioid initiation to follow-up endpoint was 7.3±6.1 patient-years. There were 196,594 (11.2%) of the 1,749,897 adult opioid users died during the study period, and the incidence rate of overall mortality was 154.6 events/ 10000 patient-years with the mean time-to-event of 5.2± 2.9 years.

For the 1,021,885 (58.4%) adult opioid users who were eligible to link with the ONS death certification, the number of patients with a record of drug-misuse death, opioid-related death, opioid-related death excluding methadone, opioid-related death excluding heroin and opioid-related death excluding both methadone and heroin was 630 (0.06%), 314 (0.030%), 286 (0.028%), 277 (0.027%) and 245 (0.024%) with the incidence rate of 0.87, 0.43, 0.40, 0.38 and 0.34 events/ 10000 patient-years, respectively. The mean time-to-events of drug-misuse deaths, opioid-related deaths, opioid-related deaths excluding methadone, opioid-related deaths excluding heroin and opioid-related

deaths excluding both methadone and heroin were 5.4±5.3, 5.9±5.7, 5.9±5.8, 6.3±5.9 and 6.4±6 years, respectively.

The number of opioid-related deaths increased from 2001 to 2013 and decreased in 2014. Between 2010 and 2012, the number of opioid-related deaths excluding heroin (deaths related to methadone or other prescribing opioids) increased steadily (from 25 to 43), but the number of opioid-related deaths excluding methadone (deaths related to heroin or other prescribing opioids) remained stable in 2010 and 2011 (29 and 30), and then increased in 2012 (41 cases), and this trend followed the national pattern of opioid-related deaths in England and Wales (Figure 26).

Figure 26. Number of opioid-related deaths and non-methadone opioid-related deaths in from 2001 to 2015



6.4.3. Serious adverse events in tramadol users

The mean follow-up duration from the first tramadol prescription between 1993 and 2010 to follow-up endpoint is 4.4±3.5 years for the 524,587 adult tramadol users. Based on the primary diagnosis, the number of tramadol users diagnosed with seizure, hypoglycaemia and hyponatremia were 1203 (0.40%), 1191 (0.40%) and 864 (0.29%). A higher number of tramadol users diagnosed with seizure (n=2429, 0.82%), hypoglycaemia (n=1537, 0.51%) and hyponatremia (n=2842, 0.95%) were found once all diagnosis within an episode of

hospitalisation were applied. The number of tramadol users diagnosed with serotonin syndrome from all diagnosis within an episode of hospitalisation was 134 (0.05%).

For both primary diagnosis and all diagnosis in an episode of hospitalisation, higher median of time-to-event for seizure, hypoglycaemia, hyponatremia and serotonin syndrome were found when compared to the mean of time-to-event, which imply a left-skewed distribution in time-to-event. The number of the incident events, incidence rate and time-to-event for seizure, hypoglycaemia, hyponatremia and serotonin syndrome identified from the primary diagnosis and any diagnosis of hospitalisation were summarised in Table 21.

For the primary diagnosis of each hospitalisation, the number of seizures, and episodes of hypoglycaemia and hyponatremia which occurred within one year after tramadol initiation were only 205 (17%), 191 (16%) and 156 (18.1%), and the majority of events identified from

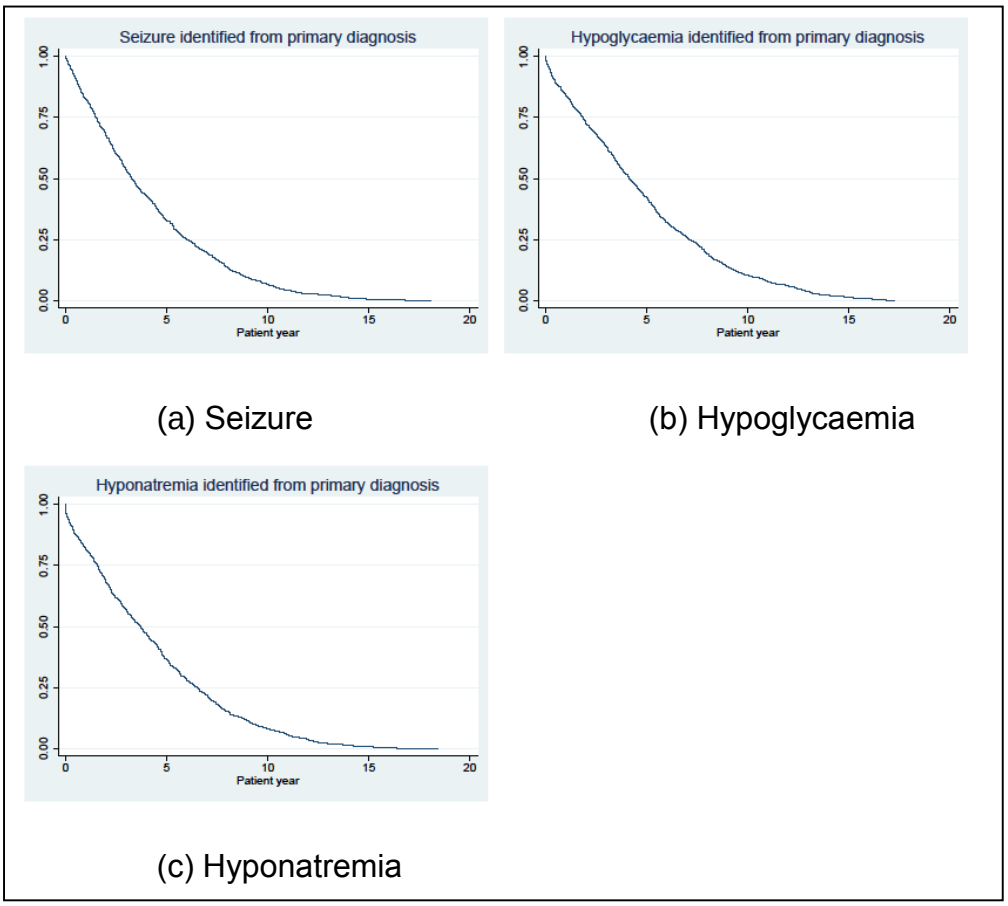
the primary diagnosis of hospitalisation happen after the first patient-year (Figure 27). Although a greater number of seizure (n=625, 25.7%), episodes of hypoglycaemia (n=364, 23.7%), hyponatremia (n=760, 26.4%) and serotonin syndrome (n=40, 29.9%) which occurred within one year after tramadol initiation were identified from any diagnosis of hospitalisation, similar to the result from primary diagnosis, the majority of events identified from any diagnosis of hospitalisation happen after the first year (Figure 28).

Table 21. Summary of the outcome measure for serious adverse events in tramadol users with linkage eligibility to HES data

	Information sources	Number of events (%)	Incidence rate *	Time-to-event (Mean± SD)	Time-to-event (Median, IQR)
Seizure	PD	1203 (0.40%)	10.3	4.2 ±3.4	3.3 (1.5, 6.1)
	AD	2429 (0.82%)	19.6	3.3 ±3.0	2.5 (0.96, 4.9)
Hypoglycaemia	PD	1191 (0.40%)	10.2	4.9 ±3.8	4.2 (1.8, 7.1)
	AD	1537 (0.51%)	13.2	3.8 ±3.3	3.1 (1.1, 5.6)
Hyponatremia	PD	864 (0.29%)	7.4	4.4 ±3.5	3.7 (1.5, 6.6)
	AD	2842 (0.95%)	24.4	3.6 ±3.2	2.7 (0.90, 5.4)
Serotonin syndrome	AD	134 (0.05%)	1.1	3.2 ±3.0	2.2 (0.85, 4.5)

(Note) PD: primary diagnosis in an episode of hospitalisation, AD: all diagnosis in an episode of hospitalisation, SD: standard deviation, IQR: interquartile range, * Incidence rate was presented in per 10000 patient-years

Figure 27. Survival curve of tramadol-related adverse events identified from the primary diagnosis of hospitalisation

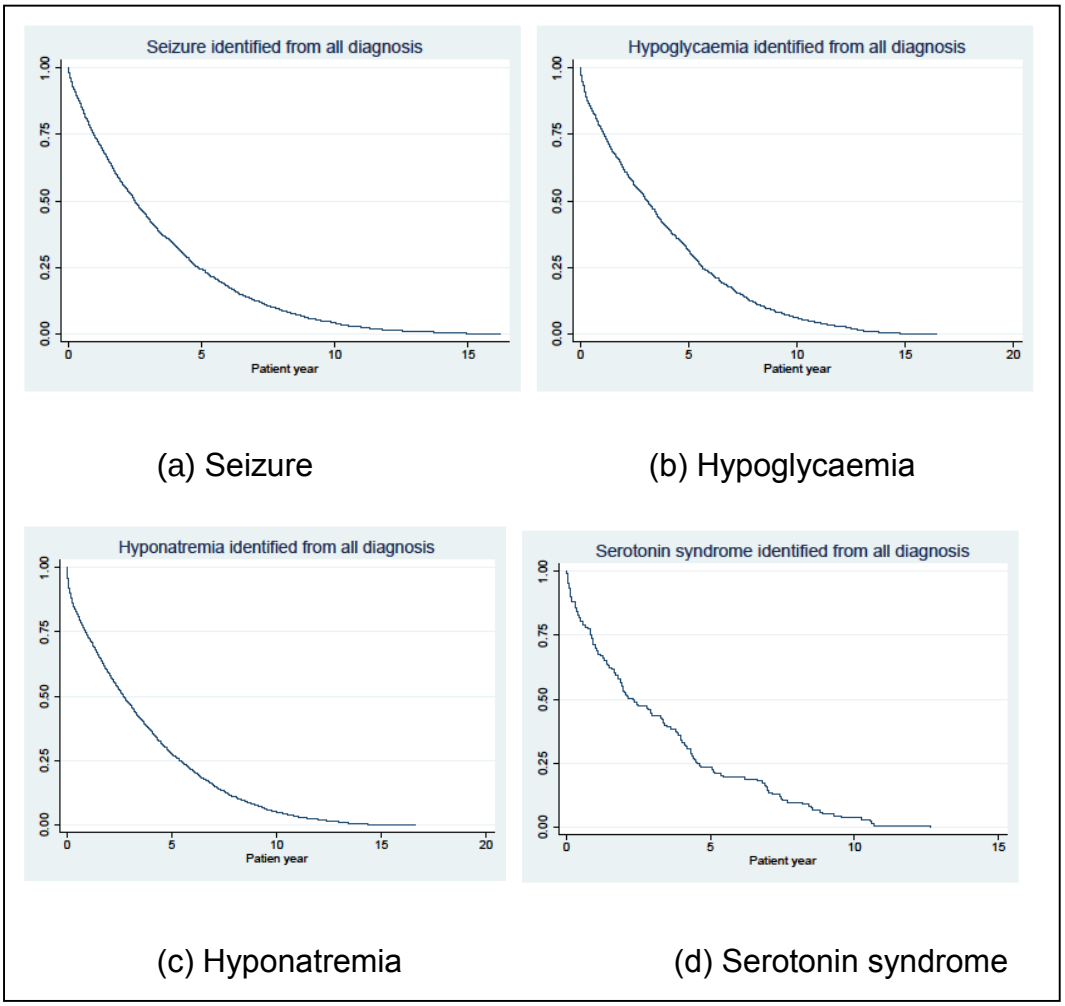


(a) Seizure

(b) Hypoglycaemia

(c) Hyponatremia

Figure 28. Survival curve of tramadol-related adverse events identified from any diagnosis of hospitalisation



6.5. Discussion

6.5.1. Main findings

The published ICD-10 codes used in the US to identify opioid-overdose death in drug-overdose death were also feasible to identify opioid-related deaths in the CPRD, and linkage ONS death certification in the UK as the trend of deaths involved individual opioids followed the pattern observed in national statistics. In addition, the published ICD-10 codes and the primary care database with the linkage to secondary care database were feasible to identify incidence rate of tramadol-related adverse events after persistent use of tramadol in the UK.

Based on the definition of frequency of adverse drug reactions from the Council for International Organizations of Medical Sciences established jointly by WHO and United Nations Educational, Scientific and Cultural Organization, the frequency of seizure and hospitalization for hypoglycaemia and hyponatremia identified from this study would be categorised as uncommon serious adverse drug reactions (≥0.1% and <1%) for tramadol users, and serotonin syndrome and opioid-related death would be categorised as rare serious adverse drug reactions

(≥0.01% and <0.1%)[254]. In addition, according to time-to-event estimated from this study, only about 20% to 30% of tramadol-related adverse events occurred within the first year after tramadol initiation, which implied the majority of tramadol-related adverse events occurred after using tramadol for a long period of time.

6.5.2. Trend of increasing opioid-related deaths

The increasing trend of opioid-related deaths identified from this study followed the trend from national statistics, which steadily increased in England and Wales between 2006 and 2009. In this study, although the number of opioid-related deaths still increased between 2010 and 2012 (decreased due to reduced availability and purity of heroin at street level around 2010 in national statistics)[25, 28], the number of opioid-related deaths excluding methadone (heroin- and other prescribing opioid-related deaths) remained stable in 2010 and 2011 and increased in 2012. In addition, the number of opioid-related deaths excluding heroin (methadone- and other prescribing opioid-related deaths) increased between 2010 and 2012. Those results implied that potential substitution effect, the number of methadone-related deaths increased

in 2011 due to ‘heroin drought’ around 2010, could also be observed in this study (Figure 26).

According to the report from ACMD, since 2012, heroin availability in street level has increased, and the number of opioid-related deaths increased 54.2% in the ONS death certification in 2015[25, 28]. However, the number of opioid-related deaths observed in this study decreased in both 2014 and 2015.

The time gap between registration in the ONS and inclusion in the linkage ONS database and the database period applied in this study caused the opioid-related deaths to be under-estimated from 2014 in this study. The linkage ONS database is a subset of original ONS death certificates, and for deaths caused by external reasons and any mental or behavioural disorder due to psychoactive substance abuse such as opioid-related deaths, a time gap between registration in the ONS and inclusion in the linkage database has been reported by CPRD[255]. As this study applied linkage ONS death certificate until December 2015, it’s

possible that the time gap between registration in the original ONS death certificate and inclusion in the linkage ONS database made the number of opioid-related deaths in 2014 and 2015 be underestimated. Therefore, although the increased trend of opioid-related death observed in this study followed the national pattern before 2013, potential under-estimates in 2014 and 2015 need to be considered when evaluating the safety of opioid utilisation as higher proportion of opioid-related deaths in the UK were involving tramadol and multiple substances in the recent years according to national ONS statistics[25].

6.5.3. The incidence of tramadol-related side effects

Gardner *et al.* (2000) conducted a cohort study in an administrative claim database between April 1995 and December 1996 after the launch of tramadol in March 1995 in the US and applied ICD-9 to investigate the occurrence of seizures among tramadol users[212]. Patients were followed from the first prescription of tramadol to the 60th day after the date of the last tramadol prescription, and the incidence rate of seizures was 6.7 events/100000 patient-days, which is about 244.55 events/ 10000 patient-years and it is higher than the incidence rate estimated from this

study (10.3 events/ 10000 patient-years from primary diagnosis and 19.6 events/ 10000 patient-years from any diagnosis)[212].

Gasse *et al.* (2000) evaluated the incidence of seizures in tramadol users between November 1996 and August 1998 after tramadol was launched in the UK in 1993 by using CPRD only rather than linking with HES, and only 21 cases were identified[168]. Compared to this study, the greater occurrence estimated from the study conducted by Gardner *et al.* might be related to the higher reported rate as prompted reporting due to the news of adverse events in the early stage after medication launched to the market has been suggested[256]. In contrast to the study conducted by Gasse *et al.* (2000) which only identified 21 cases of seizure[168], the higher number of seizures identified in this study (1203 cases from primary diagnosis and 2429 cases from all diagnosis records) highlighted the strength of applying HES to identify serious adverse events.

In addition, Jean-Pascal *et al.* (2014) have evaluated the risk of

hospitalisation for hypoglycaemia which was identified from CPRD with the linkage HES database during the first 30 days after tramadol initiation for CNCP. The incidence rate of hospitalisation for hypoglycaemia identified from primary and secondary diagnosis of hospitalisation was 7 events/ 10000 patient-years[167], which was lower than the incidence rate estimated from primary diagnosis in this study (10.2 events/ 10000 patient-years) during the study period with a mean follow-up period of 4.5 years. The results of this study indicate a higher incidence of hospitalisation for hypoglycaemia during the longer follow-up period and the need for evaluating the association between hospitalisation for hypoglycaemia and persistent tramadol utilisation.

6.5.4. The association between serious adverse events and the combination of tramadol and antidepressants

This study found the majority of seizures, and episodes of hypoglycaemia, hyponatremia and serotonin syndrome occurred after the first year after tramadol initiation, which adds knowledge to published literature measuring the incidence of serious adverse events within 90 days after tramadol initiation in the UK. However, these events

were not necessarily related to the assumption that the combination of tramadol and antidepressants caused serious adverse events.

Although increasing use of antidepressants was found associated with long-term tramadol prescribing[104, 257], the higher incidence rate of hospitalisation for hypoglycaemia observed in this study might be related to a higher incidence of comorbidity during the increasing follow-up period, such as age-related diabetes[258]. In addition, the results from the previous cohort study (Section 5.4.2, Page 165) have shown that the proportion of tramadol users received other strong opioids increased steadily from the second patient-year, and reducing seizure threshold due to other opioids was indicated in published literature[259]. In order to evaluate the association between serious adverse events and the combination of tramadol and antidepressants for persistent tramadol users, further studies should measure and adjust for potential time-dependent confounding factors.

6.5.5. The underestimated incidence rate of serotonin syndrome

The incidence rate of serotonin syndrome potentially may be under-estimated due to health care providers' lack of awareness of this condition. Being a rare adverse event, the majority of information about serotonin syndrome was documented in case reports or pharmacovigilance reports[253, 260].

The post-marketing surveillance of nefazodone was conducted in England between 1996 and 1997 by using prescribing event monitoring and questionnaire survey to identify the case of serotonin syndrome for nefazodone users and explore physicians' awareness of the syndrome[261]. For patients identified with serotonin syndrome, the results from the questionnaire survey showed that 85% of their physicians in primary care were unaware of serotonin syndrome[261]. Although there were two publications about post-marketing surveillance for tramadol, the concern was around patients with high risk of drug abuse rather than serotonin syndrome and both studies were based in the US [262, 263]. Currently, physicians' awareness of serotonin syndrome and the incidence rate of serotonin syndrome among tramadol users were still

unclear in the UK. Due to the lacking of specific diagnosis code for serotonin syndrome in current clinical classification systems, in order to develop a method to identify serotonin syndrome in healthcare database for safety evaluation, further survey identifying physicians' awareness and methods of recording tramadol induced serotonin syndrome might be needed.

6.5.6. Strengths and limitations

This is the first study to apply and validate official and reliable death certification to identify and estimate the incidence rate of opioid-related deaths in the UK. Comparing to previous publications which followed tramadol users for a short period of time and only applied CPRD to identify seizure in the UK[168, 169], this study applied linkage HES dataset and had longer study period, and hence higher number of seizure was identified. The mean time to the event of severe adverse events was more than one year, and this implied the occurrence of adverse events might be related to changes in disease condition rather than only the initiation of tramadol, and physicians should pay attention to the occurrence of adverse events even patients have been prescribed

tramadol for a long period of time.

There are limitations to this study. The linkage HES and ONS death certification only covered patients registered in the practices in England, and hence opioid-related deaths in other countries in the UK cannot be identified. In addition, there might be potential selection bias due to the differences between opioid users who were eligible to linkage data and those who were not. Nevertheless, a previous study has identified a similarity in the demographic characteristics and prescribing of medicines between practices with linkage eligibility and practices without linkage eligibility in the CPRD[264].Furthermore, the delay between registration in the ONS and inclusion in the database caused the number and the incidence of opioid-related deaths in 2014 and 2015 being under-estimated.

6.6. Conclusion and future recommendation

The linkage HES and ONS death registration and published methods were feasible to identify opioid-related deaths for opioid users and

serious adverse events in tramadol users for further safety evaluation in the UK. As serious adverse events and opioid-related death are categorised as uncommon and rare serious adverse drug reactions, further studies need to apply particular study design such as a case-control study to evaluate the safety of opioid and tramadol utilisation.

Chapter 7. A case review of opioid-related deaths and their association with short-term opioid utilisation in the UK

7.1. Introduction

Opioid-related harm is caused by the complex physical and psychological mechanism involving interactions between social determinants, pain conditions and medication-taking behaviours. A SR of observational studies aimed to identify determinants contributing to increased 'opioid-overdose deaths' between 1990 and 2013 in the US and Canada found that several factors were associated with opioid-overdose deaths in North America, including patients' demographic characteristics and disease history, prescribing behaviour and environmental and systemic determinants, such as regional prescribing policy[45].

Based on the dose-dependent mechanism of opioid-related adverse effects, such as respiratory depression[48], taking prescribing opioids in excessive amounts is considered as the main reason for opioid-overdose deaths in the US. According to the US CDC, opioid

overdose death is defined as ‘death that happens when opioid is taken in excessive amounts and caused injury to the body (poisoning)’[22]. In the US, the majority of drug-overdose deaths are caused by an overdose of prescribed opioids rather than illicit substances such as heroin[17]. In particular, a strong opioid, oxycodone, which was mainly prescribed in long-acting formulations in the North America[131], is the opioid most frequently been reported to cause opioid-overdose deaths in the US due to the relatively higher potency and releasing high dose once crushing the pills.[129].

Therefore, the majority of published epidemiological studies in the US have applied prescribing or dispensing data to evaluate the association between opioid-overdose deaths and dose of prescribed opioids. Opioid daily dose between OMEQ dose 90 and 200 mg/day in a short period before the date of opioid-overdose such as the past 90 days and the event day has been associated with opioid-overdose deaths in the North America[7, 9, 41, 42, 45]. In addition to large opioid daily dose, long-acting opioid formulations and strong opioids have also been associated with opioid-overdose mortality in studies using both individual-patient data[60,

[131, 265] and aggregate-level statistics and dataset[266] in North America.

Due to the concerns on the misuse-deaths related to heroin from 1980, the UK ONS routinely recorded drug-misuse death which is defined as 'deaths where the underlying cause is drug abuse, dependence and poisoning', and opioid-related death is a subset of drug-misuse deaths 'when an opioid was mentioned on the death certificate'[23, 24]. Compared to opioid-overdose deaths in the US, which is mainly caused by the overdose of prescribed opioids, opioid-related deaths in the UK are mostly related to drug abuse, dependence and poisoning especially heroin. Therefore, the disparity in utilisation of prescribing opioids and medication taking behaviours may be expected between patients recorded as opioid-related deaths in the UK and opioid-overdose deaths in the US.

According to the definition of opioid-related death in the UK[22-24], it is unsurprising that about 70% of opioid-related deaths in the UK involved other substances with abuse potential, such as alcohol, antidepressants

and BZDs in 2013[25]. The combination of opioids and CNS depressants, such as antidepressants and BZD and gabapentin would cause oversedation and respiratory depression even when patients are taking a low dose of prescribing opioids[13, 14].

Furthermore, in contrast to oxycodone which is the leading drug for opioid-overdose deaths in the US, heroin and morphine (60.4%) were the most frequently reported opioids in opioid-related deaths in England and Wales followed by tramadol (10.5%) and codeine (6.4%) in 2015[28]. Morphine, tramadol and codeine are less potent analgesics than oxycodone[202], and most of tramadol and codeine were prescribed in short-acting formulations in the UK. Therefore, it is reasonable to hypothesis that most of the opioid-related deaths in the UK were prescribed opioids with relative lower daily dose, less potency and short-acting formulations. However, no epidemiology study applied individual-patient data to measure opioid dose, potency and formulations for opioid-related deaths and test its association in the UK.

In addition, current recommendations to ensure safe opioid prescribing are mainly based on the evidence inferencing the association between opioid-overdose deaths and opioid use in the US, for example prescribing opioids with OMEQ dose less than 120 mg/day and prescribing short-acting opioids for less than 2 weeks have been recommended to prevent serious adverse events for patients with chronic pain in the UK[5]. However, due to the discrepancy in the definition of 'opioid-related deaths' and 'opioid-overdose deaths' between the UK and the US[22-24, 28, 129], opioid-related deaths in the UK might take prescribed opioids with lower daily doses and make the recommended dose from North America less applicable in the UK.

Furthermore, to inform guidance of prescription opioid utilisation, it is crucial to explore both patients' characteristics and utilisation of medications associated with opioid-related deaths in the UK. Current statistics of opioid-related deaths published by the UK ONS are based on the post-mortem registration, which records information from post-mortem examination, and hence except demographic characteristics, the illness and disease history (such as pain and

depression) and substances abused may not be reported[28]. Also, the prescriptions history was not reported by coroners in the UK[227], and currently the utilisation of opioids and sedatives in opioid-related deaths in the UK are unclear.

To study the epidemiology of a rare adverse event, a detailed case report can help to understand the key features of the event. In addition, case-only study designs which only include cases that are assumed to have similar characteristics to each other can evaluate medication use and its consequent outcomes by balancing risk factors between study groups[267-272]. Case-only study designs can be further categorised into the exposure-anchored study (including self-controlled case-series study) and the outcome-anchored studies (such as case-case-time control study and case-crossover study)[267-272].

Self-controlled case-series studies estimate a relative incidence of a repeatedly-happening event between exposure and non-exposure periods and assume events must not influence subsequent exposures

as post-event exposures are taken into account[271, 272]. In contrast, case-case-time control studies, one type of outcome-anchored studies, match each case period to reference periods from other cases, who do not have the diagnosis of events at the calendar time when a case is identified in order to adjust confounding factors related to calendar time such as the launch of medications[270]. However, the method of matching may potentially lead to the imbalance in risk factors between case periods and reference periods and a reduced sample size especially for cases with rare incidence[270]. The case-crossover design controls time-independent factors (such as gender) by comparing the exposure immediately before the outcome (exposure in the case period) with exposure in earlier periods (exposure in the control period) in the same person and assumes transient exposure increased the risk of events[267-269].

As published studies assume the association between opioid daily dose in a short period before the date of opioid overdose[7, 9, 41, 42, 45], prescribing guidance suggests that transient increase in opioid daily dose and opioid potency increases the risk of opioid-related deaths[5].

Although opioid-related deaths in the UK may involve several different determinants to opioid-overdose deaths in the US, this study followed US-based publications and hypothesised that opioid-related deaths are closely related to the overdose of opioids. This study took a case-crossover study design to control time independent characteristics, and analyse the relationship between opioid dose and opioid-related deaths by adjusting for the concurrent use of sedatives as a potential confounder.

7.2. Aim and objectives

This chapter aimed to investigate the relationship between opioid-related deaths and dose of prescribing opioids, characteristics and sedatives in the UK primary care setting. The objectives included:

(1) To describe the characteristics of cases of opioid-related deaths

(2) To quantify the prescriptions of opioids and sedatives before the opioid-related deaths

(3) To evaluate the association between opioid utilisation and opioid-related deaths in different person-time periods after adjusting the use of sedatives

7.3. Methods

7.3.1. Study design and database

This case-crossover study used a UK primary care database, the CPRD from January 1987 to December 2015 with the linkage to the ONS death certification from 1998 to 2015. For each patient, demographic characteristics, clinical diagnoses and prescription records were extracted from the CPRD, and the causes of death were retrieved from ONS death certification. The procedures of extracting CPRD data and linking with ONS death certification have been described in Chapter 6 (Section 6.3.2, Page 197).

CPRD is the most extensive primary care database which providing longitudinal clinical records, including demographic characteristics, clinical diagnoses and prescription records from daily practice in the UK, and hence patient characteristics and longitudinal medication utilisation in primary care could be identified[243]. Also, based on the Births and Deaths Registration Act (1836), all deaths in England and Wales related to drug poisoning should be referred to a coroner for investigation and registration, and hence the ONS death certification provided a valid,

comprehensive and the most reliable death record for the cause of death from 1998[273].

For practice registered in CPRD and consenting to participate in the linkage scheme, patients registered in the practice were linkage eligible to the ONS death certificate. This research protocol was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (Protocol number: 12_007RA).

7.3.2. Study cohort

Opioid users who died with a record of opioid-related death were defined as the study cohort. Patients prescribed with at least one oral or transdermal opioid between 2000 and 2015 were identified as an opioid user, and all records of opioid prescriptions issued with those opioid users during 1987 to 2015 were retrieved. Adult opioid users (more than 18 years on the date of the first opioid prescription issued between 1987 and 2015) who had a death record were identified.

The causes of death on ONS death certification was screened by relevant codes from ICD-10 (Appendix 6), and the definition of 'non-methadone opioid-related deaths' in the previous cohort study (Section 6.3.4, Page 203) was applied as 'opioid-related death' in this chapter. Opioid users with linkage eligibility to ONS death certification and having relevant ICD-10 diagnosis records of opioid-related deaths on the death certificate from 2000 to 2015 were identified as the cases of opioid-related deaths. This study did not include methadone-related deaths because methadone is mainly indicated for substitution therapy rather than pain control in the UK, and the change in the number of methadone-related deaths was related to the implementation of opioid substitute treatment as the equivalency of methadone vary among population[135, 138, 139, 225].

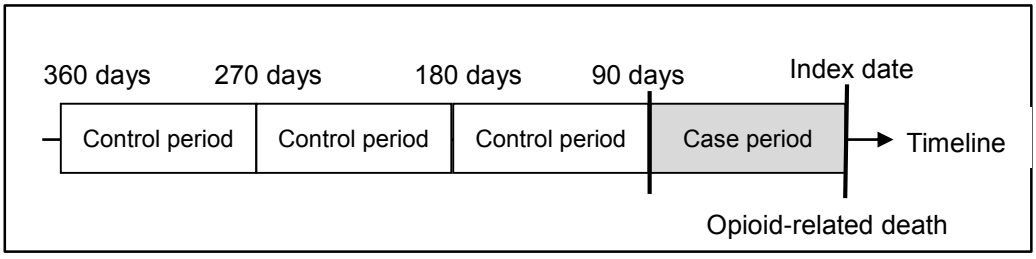
The date on the opioid-related death record was defined as the 'index date'. Patients who transferred out from the CPRD practices before the index date were excluded. Each case of opioid-related death was followed from the index date retrospectively up to 360 days, and hence patients prescribed with opioid less than one year (from the date of first

opioid prescription) before the index date were also excluded (Figure 29).

7.3.3. Case and control periods

For each case of opioid-related death, the 360-day retrospective follow-up duration was divided into one case period and three control periods. The case period was defined as 0-89 days and control periods as 90-179, 180-269 and 270-359 days before the index date (Figure 29). The duration of case and control periods were based on published case-control studies assessing the association between opioid-overdose deaths and opioid mean daily dose with the longest duration of 3 months[7, 9, 42].

Figure 29. Definitions of case and control periods



7.3.4. Demographic characteristics and disease history before opioid-related death

To understand demographic characteristics and disease history of cases with opioid-related deaths, age and gender on the index date and comorbidities associated with opioid-related deaths, such as substance abuse history, pain condition and psychological illness from one year before opioid initiation to the index date were identified.

7.3.5. Opioid and sedative utilisation

For each case of opioid-related death, prescriptions of opioids and sedatives (categorised as the list in BNF) issued in each case and control period were identified by product codes in CPRD (Appendix 14, Appendix 15 and Appendix 17) and grouped into categories by potency, formulation and pharmacology class (defined as follows). The mean daily dose of opioids and sedatives in each period were further calculated.

Opioid analgesics were classified into four categories by the potency, i.e.

weak (codeine, dihydrocodeine and dextropropoxyphene) or strong opioids (meptazinol, fentanyl, morphine, oxycodone, buprenorphine, hydromorphone, pethidine tramadol and tapentadol) as well as the formulation, i.e. long-acting (modified release and transdermal patch) or short-acting formulations. According to the ONS reports[234], medicines commonly reported involving drug-misuse deaths were retrieved by product codes in CPRD. The medications included BZDs, Z-drug, first-generation antipsychotics, second-generation antipsychotics, gabapentin/pregabalin, other (non-gabapentin/pregabalin) anticonvulsants, SSRI/SNRI, TCAs and other antidepressants.

The dose of each opioid prescription was calculated by multiplying quantity and strength (in milligrams) and then multiplying by OMEQ-conversion factors[202] to derive OMEQ dose. The quantity of each opioid prescription was divided by numerical daily dose recorded in the therapy file of CPRD to derive the number of 'supply days' for each prescription. If the interval between the dates of two consecutive opioid prescriptions was shorter than the number of supply days, the supply day was replaced by the interval between the two consecutive

prescriptions.

In each case and control period, the OMEQ dose and supply day for each opioid prescription were summed up to calculate the total OMEQ dose and supply day. If the duration of an opioid prescription covered in two consecutive periods, only the duration within each period was summed and the OMEQ dose contributed to each period was based on the proportion of supply days. The mean daily OMEQ dose in each case and control period was calculated by dividing the total OMEQ dose by the total supply day.

7.3.6. Data analysis

Descriptive statistics were used to report the demographic characteristics, disease history and utilisation of medication for opioid-related deaths. The effects of opioid utilisation on the occurrence of opioid-related death were assessed by a conditional logistic regression (CLR) model compared the case and control periods and adjusted for sedatives and potential cluster effects as the case and

control periods were identified from the same cases of opioid-related deaths and hence were expected to be similar [274]. In the CLR model, the occurrence of opioid-related death was defined as the dependent variable, and opioid use, formulation of opioid, strength of opioid, types of sedative and mean daily dose of opioid (OMEQ mg/day) and sedative during follow-up periods were included as independent variables.

Univariate analysis was applied to test the association between opioid-related death and individual variable, including opioid use (yes or no), formulation of opioid, strength of opioid, opioid mean daily dose and utilisation of sedatives. Relevant variables identified from the univariate analysis were included in the further regression analysis, and the results of the univariate analysis were presented in unadjusted odds ratios (uOR) and 95%CI. The results of the multivariate analysis were presented in adjusted odds ratios (aOR) and 95%CI.

Following the published recommendations for conducting and reporting case-crossover study[268, 275, 276], to test potential persistent users bias, a

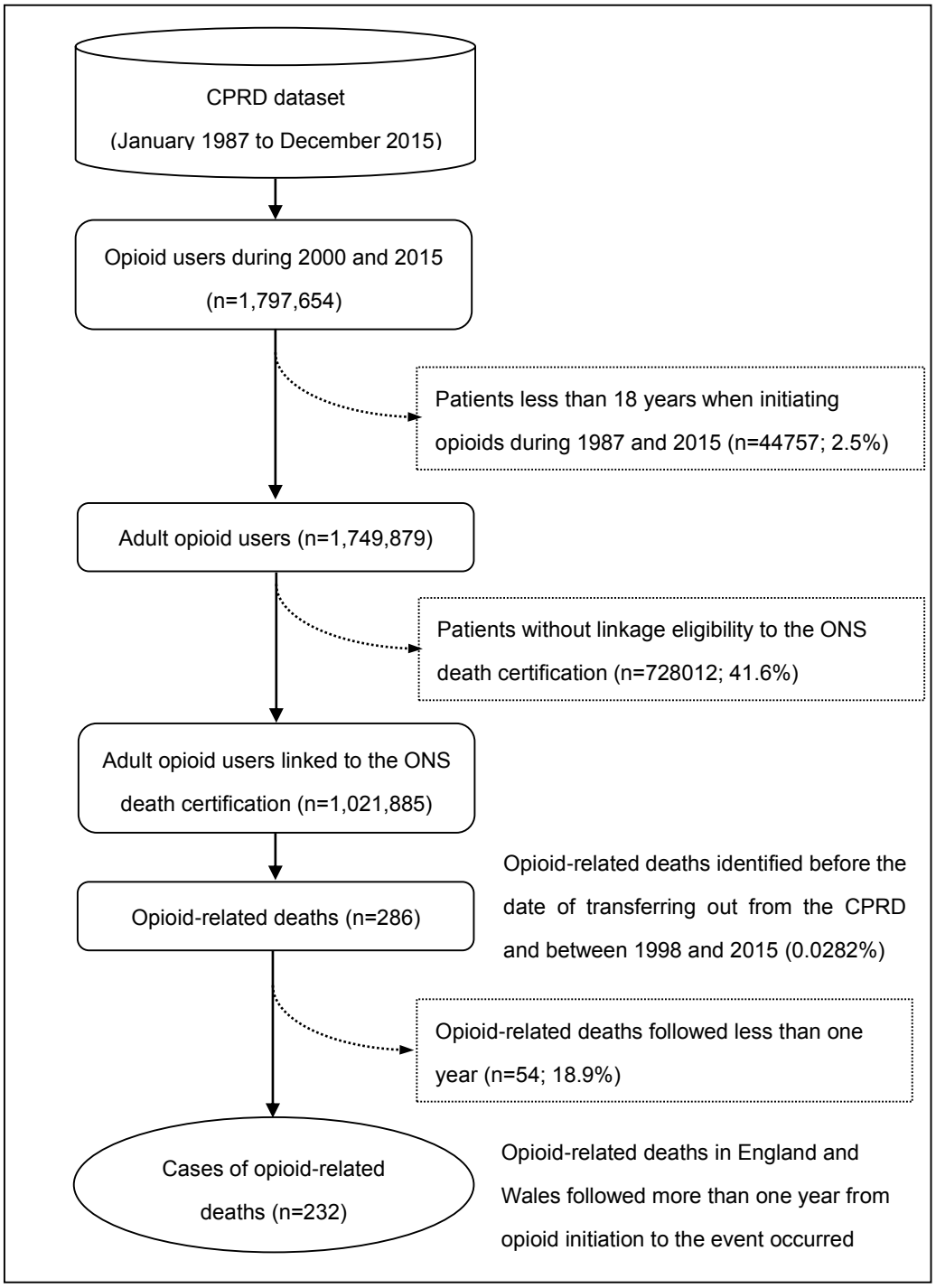
two-way sensitivity analysis was applied to check whether the change in (1) the duration of case and control periods (comparing 15, 30 and 60 with 90 days) or (2) alternation in the number of control periods (comparing 1 and 2 controls periods closed to the case period with 3 controls periods) would influence the association between opioid utilisation and opioid-related deaths derived from the CLR model.

7.4. Results

7.4.1. Selection of study cohort

Overall, 1,794,654 patients were prescribed oral or transdermal opioids between January 2000 and December 2015; and 1,749,897 (97.5%) were adult opioid users. Of the 1,749,897 adult opioid users, 1,021,885 (58.4%) were linkage eligible to the ONS death certification, and of which, 286 (0.028%) cases of opioid-related death were identified. After excluding 54 (18.9%) cases of opioid-related deaths who registered in CPRD less than one year or transferred out from the CPRD before the index date, 232 (0.023%) cases of opioid-related deaths from the 1,021,885 patients were included as the study cohort (Figure 30).

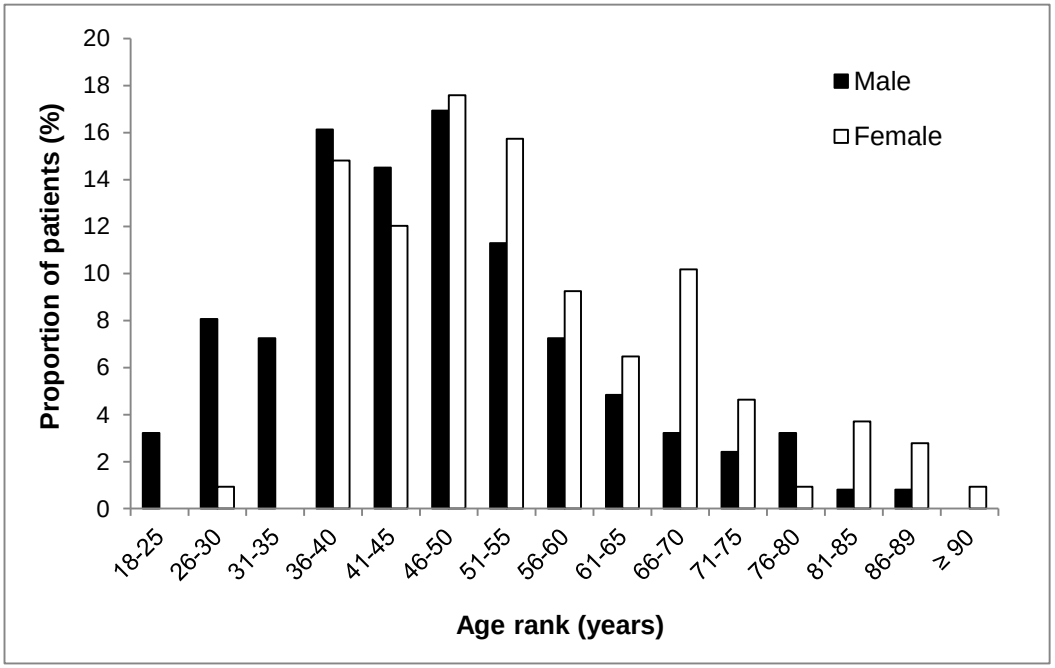
Figure 30. The process for identifying adult opioid users with a record of opioid-related death



7.4.2. Characteristics of the study cohort

Of the 232 cases of opioid-related death, 124 (53.5%) were male. The median duration from opioid initiation to opioid-related death was 5.6 (interquartile range: 2.6, 9.8) years. The majority of opioid-related-deaths occurred at the age between 35 and 55 years (n=140, 60.3%) and the median age was 49 (interquartile range: 40, 58) years. The mean age of male on the index date was significantly younger (46.9±1.2 vs 54.7±1.3, p<0.0001) than female (n=108, 46.5%) (Figure 31).

Figure 31. Age distribution for the 232 cases of opioid-related deaths stratified into male and female



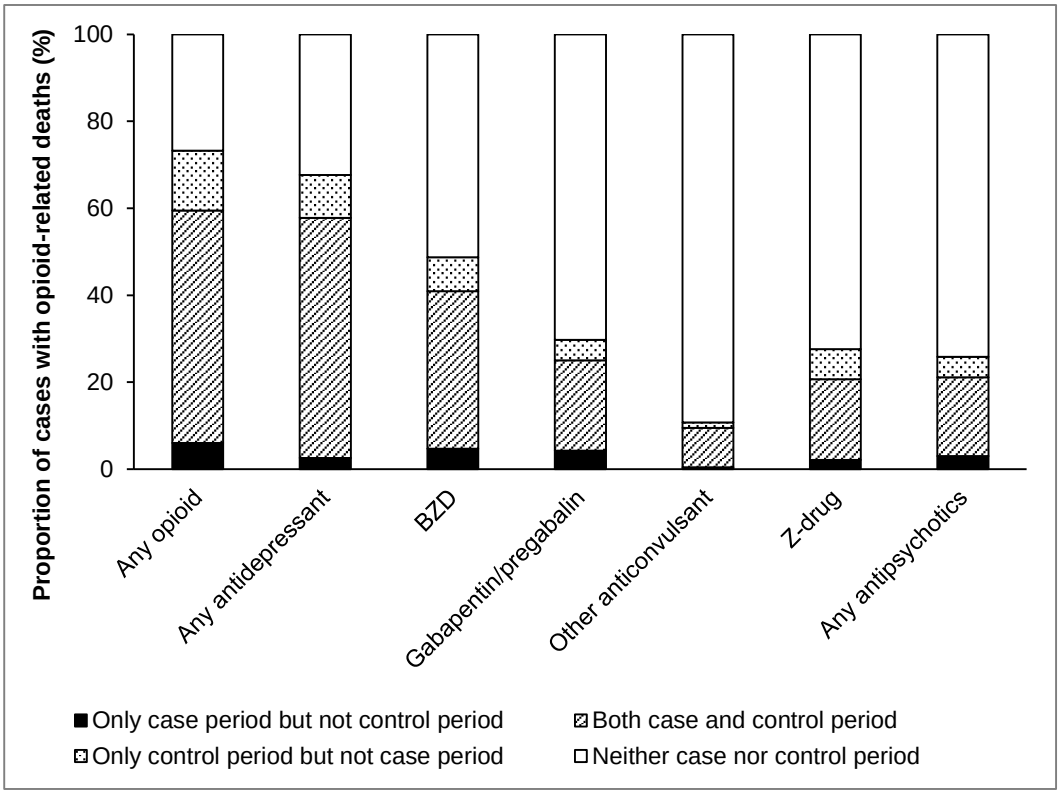
From one year before opioid initiation to the date of opioid-related death, 59 (25.4%) and 71 (30.6%) cases were diagnosed with alcohol or other substance abuse disorders. There were 23 (9.9%) and 151 (65.1%) cases diagnosed with cancer and CNCP, respectively. Low back pain (n=136, 58.6%) was the most common CNCP conditions followed by arthritis (n=36, 15.5%). In addition, there were 90 (38.8%), 51 (22%) and 20 (8.6%) cases of opioid-related deaths were diagnosed with abdominal pain, headache and migraine, respectively.

Most cases of opioid-related death (73.7%, n=171) had records of psychological consultations or were diagnosed with psychological diseases from the one year before opioid initiation to the index date, such as depression (n=126; 54.3%), sleep disorder (n=94: 40.5%) and anxiety (n=70; 31.2%). Also, 33.6% (n=78) and 11.2% (n=26) cases of opioid-related death had records of asthma and shortness of breath, respectively. Furthermore, 62 (26.7%) cases had records of drug overdose before opioid-related death and, 166 (71.6%) of opioid-related deaths had records of medication utilisation review done by general practices.

7.4.3. Opioid and sedative utilisation for individual cases

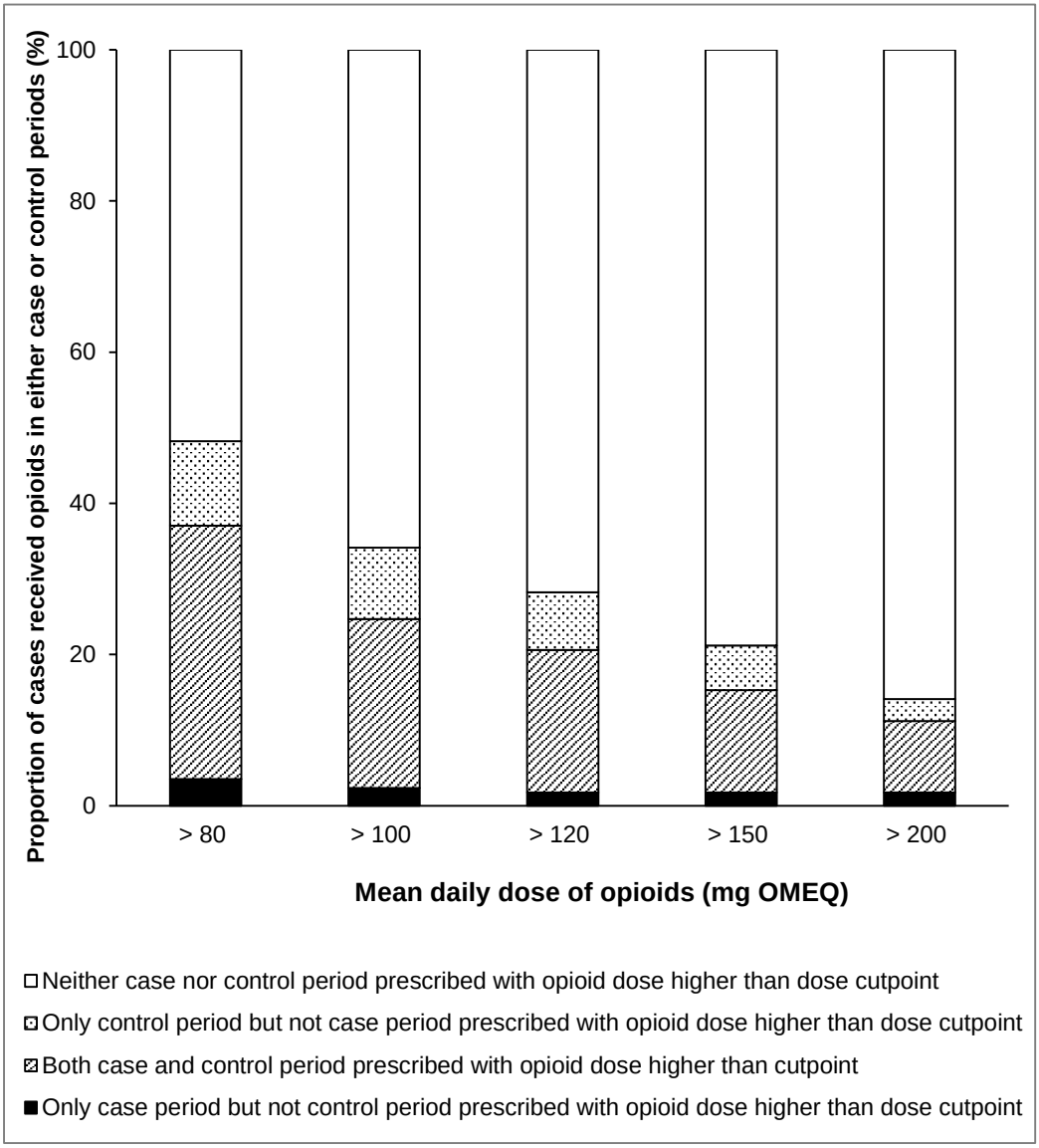
Of the 232 cases of opioid-related deaths, 170 (73.3%) cases were prescribed with opioids in the case or control periods, but 62 (26.7%) cases were not prescribed with any opioid in the one year before opioid-related death. Of the 170 cases who were prescribed opioids, 124 (72.9%) cases were prescribed opioid in both case and control periods (Figure 32).

Figure 32. Opioids and sedatives prescribed to the 232 cases in the year before the date of opioid-related death and stratified by the case or control periods



For the 170 cases prescribed with opioids in either case or control periods, just over half of them (n=88, 51.8%) were prescribed opioids with a mean daily OMEQ dose less than 80 mg/day in either case or control periods. Although OMEQ dose 120 mg/day has been recommended as the maximum daily dose of opioid prescribing due to safety concerns in the UK, 48 (28.3% of the 170 cases) cases still used opioid with a mean daily OMEQ dose more than 120 mg/day. Of the 48 cases whoever used opioids with mean daily OMEQ dose more than 120 mg/day, most (n=32, 66.7%) were prescribed a high dose of opioids in both case and control periods and only 3 (6.3%) cases had transient dose increase in case periods (Figure 33).

Figure 33. Mean daily dose of opioids prescribed in the year before opioid-related deaths among the 170 cases received opioids in case or control periods

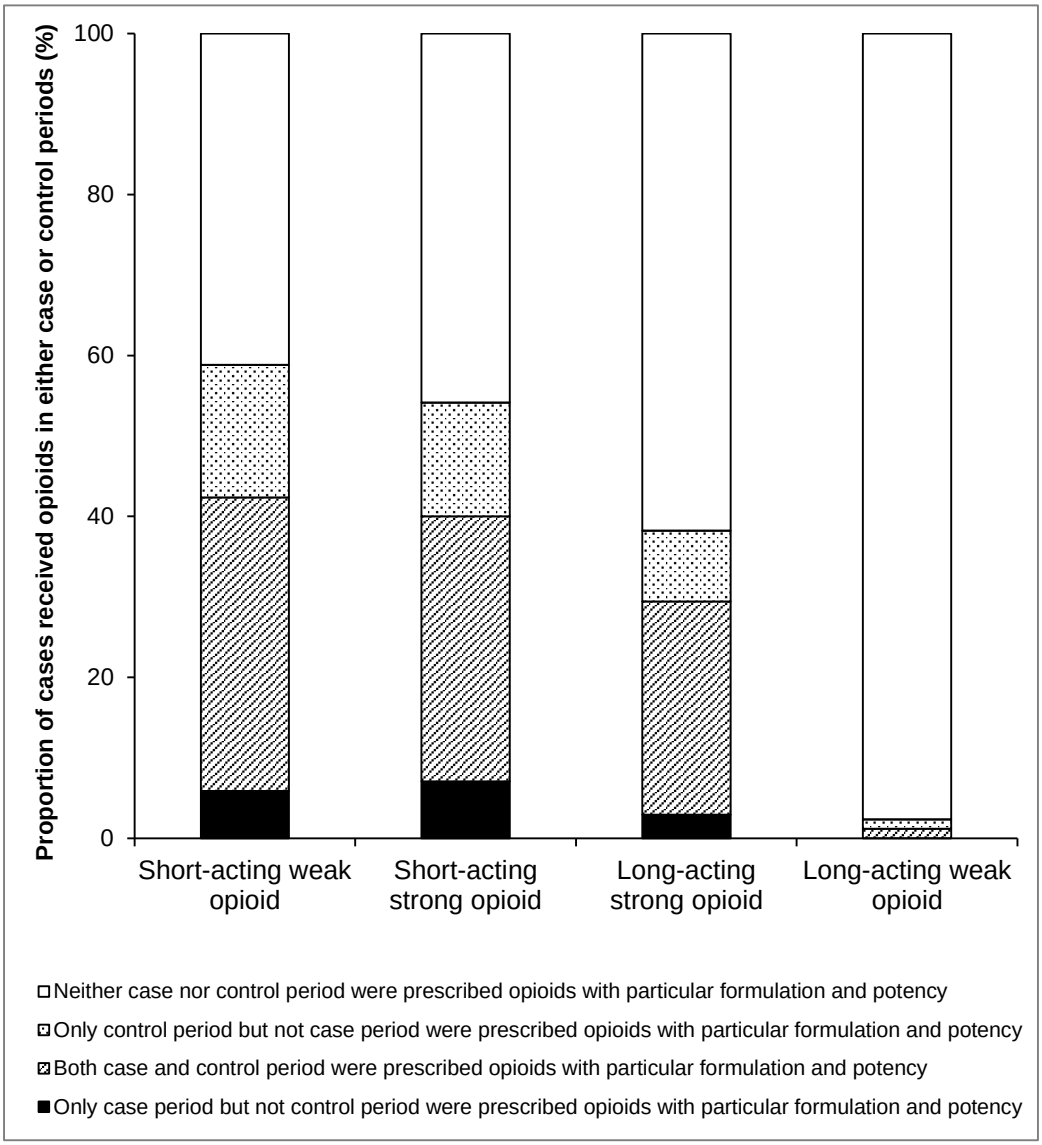


Among the 170 cases prescribed with opioids in either case or control periods, 100 (58.9%) of them were prescribed with short-acting weak opioids in either case or control periods, followed by short-acting strong opioids (n=92, 54.1%), long-acting strong opioids (n=65, 39.2%) and

long-acting weak opioids (n=4, 2.4%). Combinations of opioids with different formulations and potency were prescribed to 55 out of the 170 cases (32.4%) in either case or control periods, and of whom, the most common combination is short-acting and long-acting strong opioids (n=40, 72.7%).

Of the patients received short-acting weak opioids (n=100), short-acting strong opioids (n=92) and long-acting strong opioids (n=65) in either case or control periods, most of them used short-acting weak opioids (n=62, 62%), short-acting strong opioids (n=56, 60.9%) and long-acting strong opioids (n=45, 69.2%) in both case and control periods rather than transient prescribed in only case periods (Figure 34).

Figure 34. Formulation and potency of opioids prescribed in the year before opioid-related deaths among the 170 cases received opioids in case or control periods



There were 188 (81%) cases of opioid-related deaths prescribed sedatives in either case or control periods, and 168 of the 188 (89.4%) cases used sedatives in both case and control periods. There were 157 (67.7%), 113 (48.7%) and 69 (29.7%) cases of opioid-related deaths

received antidepressants, BZDs and gabapentin/pregabalin, respectively in the final year before death; and for patients received antidepressants, BZDs and gabapentin/pregabalin, most of them used antidepressants (n=128, 81.5%), BZDs (n=84, 74.3%) and gabapentin/pregabalin (n=48, 69.6%) in both case and control periods (Figure 32).

7.4.4. Unadjusted association between prescribed opioid utilisation and opioid-related deaths

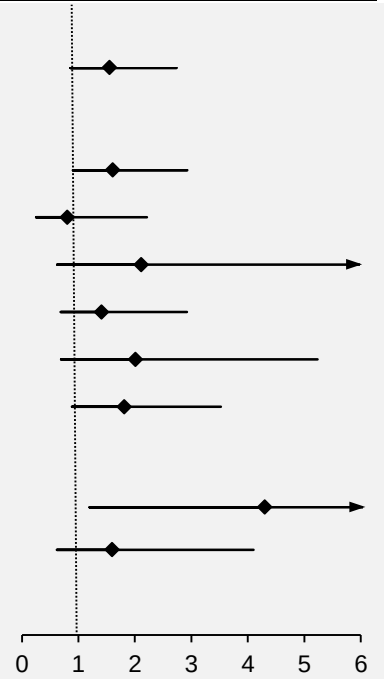
For the 170 cases prescribed opioids in either case or control periods, comparing to study periods which were not prescribed with opioids, any prescribed opioids were associated with a significantly increased risk of opioid-related death (uOR: 1.7; 95%CI: 1.0, 2.9). The study periods prescribed with only short-acting formulations had a significantly increased risk of opioid-related deaths (uOR: 1.7; 95%CI: 1.0, 3.0) when compared with periods not prescribed any opioid (Figure 35).

The study periods prescribed with mean daily opioids dose of OMEQ

dose greater than 200 mg/day were associated with a significantly increased risk of opioid-related death (uOR: 4.2; 95%CI: 1.0, 17.5) when compared with periods without any opioid prescription. However, study period prescribed with a mean daily dose of opioids for more than 120 mg OMEQ dose was not associated with opioid-related deaths (uOR: 1.6; 95%CI: 0.62, 4.1) (Figure 35).

Figure 35. Association between opioid prescriptions and opioid-related deaths by comparing the case and control periods

Opioid prescription	Unadjusted odds ratio (95%CI)
Type of opioid	
Any opioid	1.7 (1.0, 2.9)
Opioid formulation and strength	
Only short-acting opioids	1.7 (1.0, 3.0)
Both short- and long-acting opioids	0.9 (0.35, 2.3)
Only long-acting opioids	2.2 (0.72, 6.5)
Only weak opioids	1.5 (0.78, 3.0)
Both weak and strong opioids	2.1 (0.79, 5.3)
Only strong opioids	1.9 (0.98, 3.6)
Mean daily dose (MDD) of opioids	
MDD≥ 200 mg OMEQ dose	4.3 (1.2, 15.4)
MDD≥ 120 mg OMEQ dose	1.6 (0.62, 4.1)



(Note) MDD: mean daily dose, OMEQ: oral morphine equivalent

7.4.5. Association between prescribed opioids and the risk of opioid-related death after adjusting for utilisation of sedatives

The prescription of opioids was not significantly associated with the increased risk of opioid-related death (aOR: 1.6; 95%CI: 0.97, 2.7) after adjusted for prescriptions of gabapentin/pregabalin (aOR: 2.3; 95%CI: 1.0, 5.3) and other antidepressants (aOR: 3.0; 95%CI: 1.0, 9.0) (Figure 36).

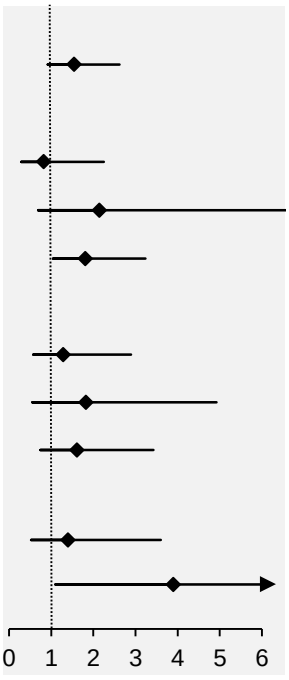
For the formulation of prescribed opioids, periods prescribed with only short-acting formulations (aOR: 1.7; 95%CI: 1.0, 3.0) were at a significantly increased risk of opioid-related death after adjusted for other antidepressants (aOR: 3.4; 95%CI: 1.1, 9.9). However, the strength of prescribed opioid was not significantly associated with opioid-related death (Figure 36).

In addition, the prescription of opioids with a mean daily dose more than 120 mg OMEQ dose (aOR: 1.4; 95%CI: 0.52, 3.6) was not associated with an increased risk of opioid-related death, but periods prescribed

with opioids with mean daily dose more than 200 mg OMEQ dose were significantly associated with an increased risk of opioid-related deaths (aOR: 3.9; 95%CI: 1.1, 14.1) after adjusted the use of gabapentin/pregabalin (aOR: 2.3; 95%CI: 1.0, 5.3) (Figure 36).

Figure 36. Association between utilisation of prescribed opioids and opioid-related death by comparing the case and control periods and adjusting for the prescription of sedatives

Opioid prescription	Adjusted odds ratio (95%CI)
Opioid use	
Any opioid	1.6 (0.97, 2.7)
Formulations	
Taking both short- and long-acting opioids	0.79 (0.3, 2.1)
Only taking long-acting opioids	2.0 (0.67, 6.1)
Only taking short-acting opioids	1.7 (1.0, 3.0)
Strengths	
Only taking weak opioids	1.4 (0.73, 2.9)
Taking both weak and strong opioids	1.9 (0.71, 4.8)
Only taking strong opioids	1.7 (0.89, 3.4)
Mean daily dose (MDD) of opioids	
120≤ MDD mg OMEQ dose	1.4 (0.52, 3.6)
200≤ MDD mg OMEQ dose	3.9 (1.1, 14.1)



(Note) MDD: mean daily dose, OMEQ: oral morphine equivalent

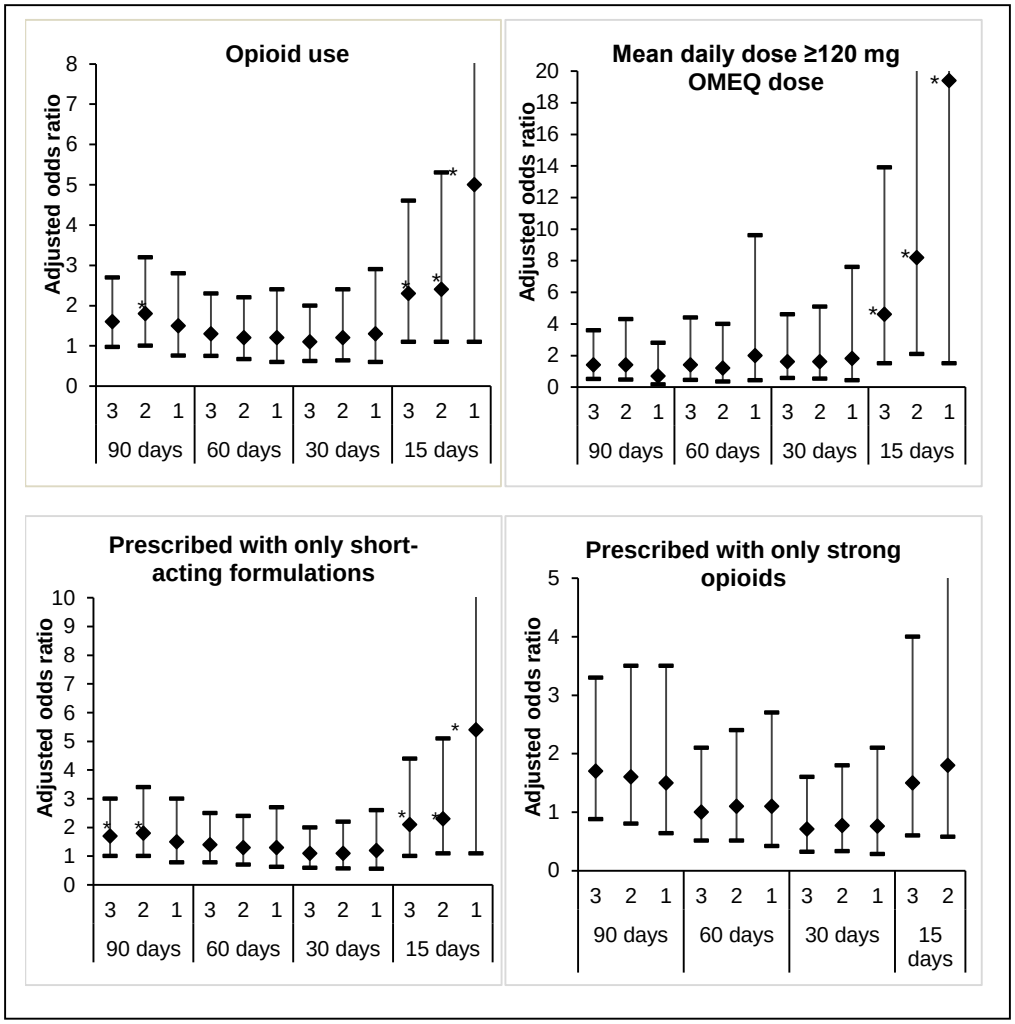
7.4.6. Sensitivity analysis

When the duration of case and control periods were defined as 90 days,

most of the significant associations identified in the CLR remained consistent despite changed the number of control periods in the sensitivity analysis.

However, prescription of opioids was significantly associated with opioid-related deaths when only two control periods close to the case period were included in the CLR. Also, once changing the duration of case and control periods to 60, 30 and 15 days, prescription of opioids and prescribed opioids with a mean OMEQ daily dose more than 120 mg were significantly associated with opioid-related deaths when the duration of case and control periods was 15 days. However, a wider 95%CI was also found when the duration of case and control periods became shorter (Figure 37).

Figure 37. Sensitivity analysis tested the duration of case and control periods and the number of control periods



(Note) The x-axis scale means the duration of the case and control periods and the number of control periods closed to the case period, * $p<0.05$.

7.5. Discussion

7.5.1. Main findings

This study found that opioid-related death is not associated with a high daily dose of prescription opioids. More than 70% of cases who were prescribed opioid in the final year never received mean daily dose of opioids for more than 120 mg OMEQ dose in either case or control periods, and hence it is not surprising that mean daily dose more than 120 mg OMEQ dose was not significantly associated with opioid-related deaths. However, a significant risk of opioid-overdose deaths was found when the mean daily dose was more than 200 mg OMEQ dose, and the result was similar to a cohort study in the US[41] and a nested-case control study in Canada[42] demonstrated a significant association between opioid-overdose deaths and prescribing opioids once the mean daily dose was more than 200 mg OMEQ dose.

For opioid-related deaths prescribed opioids within the final year, most of them prescribed with opioids at least one quarter. Compared to the long-acting formulation, short-acting formulation of opioids was more commonly prescribed with the cases of opioid-related deaths, and the

study periods prescribed with only short-acting formulations of opioids were found to have a greater odds of opioid-related death. Those results indicated that cases of opioid-related deaths in the UK had a long history of receiving opioids and were mainly prescribed opioid with short-acting formulations and lower dose than the dose found associating with opioid-overdose deaths in the US.

In addition, more than 80% of opioid-related deaths were regularly prescribed with sedatives within any quarter of the final year. The increased odds of opioid-related death for the prescriptions of gabapentin/ pregabalin and other antidepressants also proofed the concept that sedatives need to be considered when evaluated the association between opioid-related death and opioid utilisation. In fact, about 25% of cases of opioid-related deaths were not prescribed with any opioid, which imply the concerns about opioid diversion and abuse. Especially, this study found over 80% of opioid-related deaths happen in their middle age and most of them were diagnosed with alcohol abuse disorders (25.4%), other substance abuse disorder (30.6%), psychological illnesses (73.7%) or had a history of overdose of any

medication (26.7%).

7.5.2. Maximum prescribing dose threshold and opioid-related deaths

The results of this study are not directly comparable to previous publications that explored the association between opioid-overdose deaths and daily dose, potency and formulations of prescription opioids in the North America[7, 9, 41, 42, 44, 277] due to the discrepancies in study designs, outcome identification, opioid prescription and practice environment in different countries. This study did not find a significant association between opioid-related death and prescribing opioids with a daily dose more than 120 mg OMEQ dose which has been identified associating with opioid overdose in the previous studies using IPD in North American[41, 42, 44]. Reasons related to the opioid epidemic, other sedatives and potential substance abuse disorders might explain the discrepancies in the results between this study and previous publications.

First of all, compared to the heroin market in the US which is dominated by low-cost Colombian-sourced heroin[278], the heroin market in the UK was mainly dominated by high-purity heroin from Pakistan and Afghanistan[26, 27]. Therefore, compared to drug-overdose deaths in the US which were primarily related to the poison of prescribing opioids[17], 45.2% of drug-misuse deaths were reported involved heroin in 2015, and the trend of opioid-related deaths was paralyzed with the death involved heroin/morphine in the UK[28]. The result from this study also provided evidence that the majority of opioid-related deaths in the UK never received mean daily dose of opioids for more than 120 mg OMEQ dose.

7.5.3. Gabapentin/ pregabalin prescribing and the association between opioid-related death and opioid daily dose

Moreover, the non-significant association between opioid-related deaths and receiving opioids with a daily dose more than 120 mg OMEQ dose might be influenced by the difference in confounding factors between study periods, such as gabapentin/ pregabalin prescribing was significantly associated with opioid-related deaths in the CLR model.

A nested case-control study in Canada also found a higher dose of gabapentin in the 120 days preceding the date of opioid-overdose death was associated with an increased risk[44]. Respiratory depression has been observed when gabapentin was used alone or combined with other medication[14], and the UK Medicines and Healthcare products Regulatory Agency has advised the potential risk of respiratory depression of gabapentin in 2017[279]. Further studies evaluate the association between opioid-related deaths and opioid utilisation should adjust the influence of gabapentin/ pregabalin prescribing.

7.5.4. Non-prescribing routes of opioid consumption

The majority of opioid-related deaths identified in this study had a long history of receiving opioids. Persistent opioid users are more likely to use sedatives such as BZDs and gabapentin/ pregabalin concurrently as opioid prescribing durations were longer among persistent opioid users. In addition, persistent opioid utilisation increased the risk of substance abuse disorders[6] and cases of opioid-related deaths who did not receive any opioid in this study also indicate concerns about opioid diversion, transfer of opioid preparations from a lawful to an unlawful channel of

distribution which has been treated as one of the criteria of opioid abuse[280]. Additional sources of prescribing opioids would lead to misclassification of exposure and hence induced a non-differential misclassification error once there is a difference in the outcomes between study groups[281, 282]. Although about 25% of opioid-related deaths were diagnosed with substance abuse disorder in this study, the records of diagnosis of substance abuse disorder in the CPRD and the method applied to identify substance abuse disorder were not validated[283]. In order to identify patients who might have opioid from non-prescribing routes, additional information sources, such as the National Drug Treatment Monitoring System (NDTMS) dataset from Public Health England might link to CPRD.

7.5.5. Strengths and limitations

This is the first study applied the case-crossover study design to evaluate the association between opioid-related deaths and opioid utilisation in the UK. In addition, primary care longitudinal data was applied to identify demographic characteristics and disease history, quantify analgesic medicines commonly used for pain control and

evaluated its association with opioid-related deaths.

Compared to published case-control studies with a lack of balance in risk factors between study groups[7, 42], time-independent characteristics were controlled by selecting case and control periods from the same patients in the case-crossover study design. Furthermore, the results about exposure between case and control periods were reported in this study to identify potential persistent opioid use, which was in compliance with the reporting suggestion[275]. To identify the influence of potential misclassification of exposure and persistent user bias, a sensitivity analysis was conducted to test the influence of the duration of case and control period and the number of control periods on the association between opioid-related death and opioid utilisation.

However, the case-crossover study design may not be appropriate to evaluate the association between opioid-related deaths and time-independent confounders such as gender. In addition, the method of control group selection might also cause the non-significant difference

in opioids mean daily dose between study periods as case and control periods were selected from the same patients and some characteristics associated with opioid utilisation, such as gender were time-independent characteristics or chronic conditions[267-269].

Furthermore, although the feasibility of applying the ONS death certificate to identify opioid-related deaths has been shown in the previous chapter (Section 6.4.2, Page210), only about 60% of opioid users in the CPRD were linkage eligible to the ONS death certificate and all of them were from the practices in England and Wales[273]. Also, about 20% of cases of opioid-related deaths who were prescribed with opioids for less than one year were excluded from this study. In addition to the reduced sample size and caused the non-significant estimates, the characteristics, medication utilisation and its association with opioid-related deaths derived from this study cannot be applied to this group of patients. Furthermore, the measurements of opioid utilisation, such as opioid daily dose were based on prescribing data rather than the amount of actual consumption, and we assumed that patients took medications as prescribing records and hence potential misclassification

of exposure might happen because of non-adherence.

In addition, persistent user bias in the case-crossover study design would make a non-significant result. Once patients with exposure or unexposed in both case and control periods, they were less weighted or even not included in the CLR model as case and control periods were selected from the same patients and would be treated as a cluster in the CLR model[274]. Therefore, the reduced sample size induced an unprecise and non-significant result estimate[268]. For opioid-related deaths ever prescribed opioids with a mean daily dose more than 120 mg OMEQ dose, the majority of them had been prescribed in both case and control periods. Therefore, the non-significant association between receiving an opioid mean daily dose of more than 120 mg OMEQ dose and opioid-related deaths might be induced by persistent user bias.

As the probability of exposure changed based on the duration of case and control periods and the number of control periods, a two-way sensitivity analysis was conducted to test the influence of duration and

number of observed periods on the occurrence of persistent user bias. Although prescribed opioids with mean daily dose more than 120 mg OMEQ dose were significantly associated with opioid-related deaths once the duration of case and control periods was equal to 15 days in the sensitivity analysis, the wider 95%CI of estimated OR implied a more unprecise estimate and more severe persistent user bias. Currently, there was no optimal method to deal with persistent user bias[284], and hence the estimated association from this study should be treated with caution.

7.6. Conclusion

In contrast to the results from studies evaluating the risk factors associated with opioid overdose deaths in the US, most opioid-related deaths in the UK were prescribed opioids with lower daily dose and short-acting formulations for a long period. Furthermore, most of the opioid-related deaths were diagnosed with risk factors of opioid-overdose deaths, such as substance abuse disorder and psychological illnesses. The increased risk related to gabapentin/ pregabalin prescribing and the non-significant association between

transient opioid use and opioid-related deaths imply other medications are contributing to opioid-related deaths. Further studies should explore the association between opioid-related deaths and persistent opioid utilisation after adjusted patient characteristics and utilisation of sedatives.

Chapter 8. Association between persistent opioid utilisation and opioid-related deaths in the UK primary care

8.1. Introduction

The previous study of opioid-related mortality using a UK primary care database (Chapter 7) showed that the OMEQ dose more than 120 mg /day was not significantly associated with opioid-related death, despite current practice guidance for chronic opioid prescribing in the UK recommends prescribing opioid daily dose less than 120 mg OMEQ for safety concern in chronic pain care [3, 5, 19]. In addition, the previous study also found more than half of opioid-related fatalities received opioid prescriptions between 91 to 360 days before opioid-related death and thus implied persistent opioid utilisation rather than current opioid daily dose would be a potential determinant for opioid-related deaths.

Persistent opioid utilisation has been found to be associated with increased risks of opioid tolerance and dependency[6]. According to WHO, tolerance is defined as the reduction in response to a drug after continued use[108]. In order to achieve the original response, an increased

dose is often required when patients developed tolerance[109]. However, increasing opioid prescribing due to opioid tolerance was associated with increased risks of aberrant opioid behaviour, such as misuse and diversion which were both indicators of opioid abuse and associated with an increased risk of opioid-related deaths[6, 25, 280].

The results from the previous study (Chapter 7) found a quarter of opioid-related deaths in the UK were never prescribed opioids within the final year before opioid-related death, implying that those opioid-related deaths may be related to aberrant opioid behaviours, such as misuse and abuse of opioids. For example, failure to follow prescribed dosing or taking remaining opioids from previous prescriptions may indicate potential opioid misuse[122].

Furthermore, patients who did not receive any opioid in the final year before opioid-related deaths also imply these individuals may have acquired opioids from additional non-prescribed routes, and this opioid diversion, the transfer of opioids from a lawful to an unlawful channel of

distribution or use, is one of the criteria to define opioid abuse, and it increased the risk of opioid-related deaths in the UK[25, 280].

In addition to aberrant opioid behaviour, the change in opioid tolerance also increased the risk of opioid-related deaths for persistent opioid users. Persistent opioid users might further develop opioid tolerance and escalate to highs dose due to continued use, but discontinuation of opioid treatment may improve opioid tolerance, and a lower dose is needed[109].

However, once patients are unaware of decreased opioid tolerance and still self-administer opioids using the previous higher dose for further pain episodes, this may increase the risk of opioid-related deaths. In the UK, for prisoners who have been using a large amount of drugs before imprisonment, the decreased tolerance after an abstinence period during imprisonment has been found to be associated with an increased risk of drug-misuse death in the first two weeks after release from prisons[285, 286].

To evaluate the association between opioid-related deaths and persistent opioid utilisation, the impact of switching pattern between persistent and non-persistent opioid utilisation should also be evaluated. The previous cohort study (Chapter 4) found that patients who ever used opioid persistently were likely to remain persistent users, but some individuals switched between persistent and non-persistent opioid utilisation due to the nature of their chronic pain, and this is consistent with findings from other published cohort studies[39, 40].

In the other chronic conditions (e.g. diabetes and hyperlipidaemia), the different trajectory of patients' adherence to medicines has been associated with different treatment outcomes[287, 288]. Nevertheless, the association between opioid-related deaths and the pattern of persistent opioid utilisation in relation to aberrant opioid behaviour and opioid tolerance remains unclear.

Opioid-related deaths may also cause by the interaction between opioids and other sedatives. The interaction between opioids and CNS

depressants, such as antidepressants, gabapentin and BZDs may increase the risk of oversedation and respiratory depression induced by opioids, even when patients were prescribed with a relatively low opioid dose[13, 14, 43, 44, 289]. Persistent opioid utilisation is associated with opioid abuse[6, 280], and opioid abusers are often found to abuse multiple substance[25]. In fact, the combination of BZDs and opioids has been treated as an indicator of opioid abuse disorder[220, 290].

In the previous chapter (Chapter 5), persistent opioid users were found more likely to combine other sedatives and receive a higher mean daily dose of concurrent sedatives for more extended periods of time compared with non-persistent opioid users. The majority of studies evaluated the association between opioid-overdose deaths and the combination of opioids and sedatives in North America only quantified concurrent sedatives for short-periods of time[13, 14, 43, 44, 289].

However, the results from the previous case study (Chapter 7) found more than 80% of opioid-related deaths were regularly prescribed with

sedatives within the final year. Currently, the association between opioid-related death, persistent opioid utilisation and its long-term interaction with concurrent sedatives is still unclear in the UK[23, 24].

Opioid-related death is a rare (frequency ≥0.01% and <0.1% defined by the Council for International Organizations of Medical Sciences [254]) and very serious adverse event for opioid users. To identify the association between drug exposure and a rare adverse event, a nested case-control study design has been recommended as an efficient approach[291].

In the case of assessing the relative risk of opioid daily dose on opioid-overdose deaths, a control group matching to the cases with opioid-overdose death is needed to control potential confounding factors[291], such as demographic characteristics, disease history, medication utilisation and systemic determinants, such as Prescription Drug Monitoring Programs (PDMPs) that were associated with 'opioid overdose deaths' in studies conducted in US and Canada[7, 9, 42, 45, 130, 221, 277, 289, 292-294].

To achieve a balance of multiple factors associated with opioid-overdose death between case and control groups, Gomes *et al.* (2011) applied a disease risk score which is the probability of opioid-overdose deaths in the study cohort predicted by factors associated with opioid-overdose deaths to summarise likelihood of opioid-overdose deaths and applied it in the matching process in a nested case-control study in Canada[42, 295]. However, it is still unclear whether disease risk score could apply in the matching process in the UK.

8.2. Aim and objectives

This chapter aimed to explore the association between persistent opioid utilisation and opioid-related deaths in the UK. The objectives included:

(1) To identify an optimal control group matched with the cases of opioid-related deaths by applying disease risk score

(2) To quantify persistent opioid utilisation between the cases of opioid-related deaths and their matched controls

(3) To compare the pattern of persistent opioid utilisation between cases of opioid-related deaths and their matched controls and adjusted potential confounding factors

8.3. Methods

8.3.1. Study design and cohort

This nested case-control study used the UK CPRD from 1987 to 2015 with the linkage to the ONS death certification (data specification was described in Section 4.3.1, Page 116 and Section 6.3.1, Page 195). CPRD is the largest verified primary care longitudinal database which provides prescription records and clinical diagnosis that are required for this study. The causes of deaths, including all opioid-related deaths were retrieved from the ONS death certification because all deaths in England and Wales are registered in the ONS death certification according to the Births and Deaths Registration Act (1836)[273].

To identify the study cohort, all CPRD registrants eligible to link with ONS death certification and prescribed with opioids between 2000 and 2015 were identified. The selected eligible population were followed from the date of opioid initiation (the date of the first opioid prescription issued between 1987 and 2015) to the date of death, the end of registration or the end of study (31st of December 2015), whichever comes first. Patients followed more than one year after opioid initiation

and aged more than 18 years when the opioid was initiated were included as the study cohort.

8.3.2. Case and control identification

The definition of 'non-methadone opioid-related deaths' in the previous cohort study (Section 6.3.4, Page 203) was applied as 'opioid-related death' in this study. The incident cases of 'opioid-related deaths', i.e. study cohort who had an opioid-related death record identified from the ONS death certification (Section 6.3.4, Page203) (Appendix 6) between 2000 and 2015, were defined as the 'cases' in this study, and the date of this opioid-related death record from ONS death certificate was defined as the 'index date'.

For each case, four matched controls were selected by incident density sampling[296] without replacement, i.e. selecting patient-time when patients in the study cohort did not have the diagnosis of opioid-related death at the time when a case was identified, and patient-time could only be selected once. As the number of cases was expected to be limited,

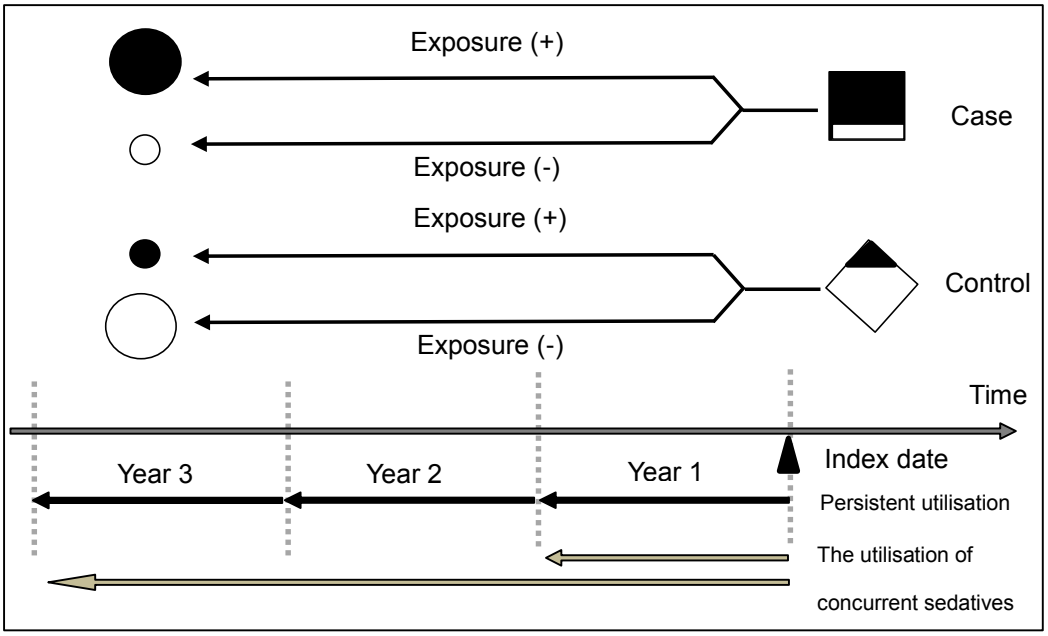
the match ratio of 1:4 was chosen to increase the precision of risk estimation. The ratio beyond 1:4 was not considered as literature has suggested that this ratio does not increase statistical power and the added value is marginal[297]. Each control was assigned the same index date with the matched case.

Cases and controls were matched on the disease risk score[295] by the nearest-neighbour matching with a calliper of 0.01, i.e. matching patients from the closest one regarding disease risk score and in the range of 0.01 to avoid unbalance matching[298]. In this study, the disease risk score was defined as the probability of opioid-related deaths in the study cohort predicted by a logistic regression model considering factors which were potentially related to opioid-related deaths and identified in one year before the index date. The patient characteristics, such as demographic characteristics[45, 130, 221, 277, 294], psychological illnesses[7, 9, 130, 289, 292, 293], substance abuse history[7, 9, 42, 130, 289, 292, 293] and pain conditions[7, 9, 130, 293] which have been suggested to be associated with opioid-overdose deaths in literature were included in the prediction model (Appendix 9).

8.3.3. Exposure to opioids and sedatives

For each case and its matched controls, prescriptions of oral and transdermal opioids (according to the list in the BNF) and sedatives (Section 7.3.5, Page 242) were identified retrospectively from index date up to three patient-years to measure the pattern of persistent opioid utilisation between opioid-related deaths and matched controlls. Persistent opioid utilisation was measured annually in the three patient-years of the retrospective follow-up period, and the mean daily dose of concurrent sedatives was measured when the sedative prescriptions are overlapping with opioid prescriptions during the one and three patient-years of the retrospective follow-up period (Figure 38).

Figure 38. The conceptual framework of study design and exposure measure timeframe



Opioid prescriptions were identified and used to measure the persistence of opioid utilisation in each patient year defined by the MDA developed by Svendsen *et al.* (2011)[39]. 'Annual opioid dose' (AD) in OMEQ dose, 'number of opioid prescriptions' (NP) and 'number of quarters covered with opioid prescriptions' (NQC) were measured annually in the three retrospective patient-years from index date to define current persistent opioid users (NQC≥3 and AD≥4500 mg OMEQ) and grouped into different definition groups (Table 22). The proportion of persistent opioid users into each definition group in case and control groups during the one and three patient-years of the retrospective

follow-up period was calculated.

Table 22. Definition of persistent opioid utilisation

Group of persistent opioid utilisation	AD	NP	NQC
Wide	≥ 4500 mg OMEQ		≥ 3
Intermediate	≥ 9000 mg OMEQ		4
Strict	≥ 18000 mg OMEQ	≥10	4

(Note) AD: Annual opioid dose, NP: number of opioid prescriptions, NQC: number of quarters covered with opioid prescriptions, OMEQ: oral morphine equivalent

The mean daily dose of concurrent sedatives when opioid and sedatives prescriptions were overlapping was measured during one and three retrospective patient-year, respectively. The definitions and methods to measure the mean daily dose of concurrent sedatives when opioid and sedatives prescriptions overlapping have been described in Chapter 5 (Section 5.3.5, Page 159). The mean daily dose of BZDs, gabapentin/pregabalin and TCAs when concurrently used with opioids were further categorised into different groups (TCAs: 0< to ≤0.5 DDD and >0.5 DDD; BZDs and gabapentin/pregabalin: 0< to ≤1 DDD and >1 DDD) according to the distribution and the performance of regression model.

8.3.4. Characteristics of the study cohort

Demographic characteristics, including age, gender and Townsend score, psychological illnesses, substance abuse and pain conditions in the year prior to opioid initiation were identified to describe the characteristics of the study cohort. Any cancer record before opioid initiation was also identified. Psychological illnesses included anxiety, depression, schizophrenia, PTSD and sleep disorder. Pain conditions included chronic pain conditions including low back pain, neuropathic pain, arthritis and fibromyalgia and other pain conditions (abdominal pain, kidney stone, migraine, pancreatitis, pelvic pain, post-operative pain and headache) (Appendix 16).

8.3.5. Data analysis

Descriptive statistics were used to report characteristics of the study cohort at opioid initiation. To evaluate the performance of matching on disease risk score, Chi-square test and t-test were used to test the difference in patient characteristics in the year before index date between case and control groups. To identify the potential association between persistent opioid utilisation and opioid-related deaths, the

proportion of persistent opioid users in each definition group between case and control groups in three and one years before the index date was also tested by the Chi-square test.

Conditional logistic regression[274] was used to assess the association between opioid-related deaths (the dependent variable) and persistent opioid utilisation in the first retrospective patient-year (independent variables) and adjusted for the use and mean daily dose of concurrent sedatives in the first retrospective patient-year. The full regression model included independent variables and all potential confounding factors, and then the results of a parsimonious model, which contained particular variables after elimination of non-significant terms were considered[299]. The risk of opioid-related deaths was presented in aOR and 95%CI.

8.3.6. Sensitivity analysis

A sensitivity analysis was conducted to test the association between different patterns of opioid persistence and opioid-related death after adjusting for the utilisation of concurrent sedatives in the three

retrospective patient-years. As persistent opioid utilisation was identified annually, eight patterns could potentially occur during the three retrospective patient-years. Assuming that persistent opioid utilisation in the first retrospective patient-year was more related to opioid-related death due to respiratory depression, persistent opioid utilisation in any of the three patient-years was group into three patterns (Table 23).

The association between opioid-related deaths and each pattern of persistent opioid utilisation was tested by individual CLR models after adjusting for confounding factors. The risk of opioid-related death associated with the individual pattern of persistent opioid utilisation was presented as aOR and 95%CI.

Table 23. Definition of the patterns of persistent opioid utilisation in the three retrospective patient-years

Definition		Retrospective patient-year		
		1st	2nd	3rd
Persistent use in any of the three patient-years	(a) In the second or third but not in the first patient-year	-	-	Persistent
		-	Persistent	-
		-	Persistent	Persistent
	(b) In the first patient-year	Persistent	-	-
		Persistent	-	Persistent
		Persistent	Persistent	-
	(c) In all the three patient-years	Persistent	Persistent	Persistent
Non-persistent opioid utilisation		-	-	-

8.4. Results

8.4.1. Baseline characteristics of study cohort when opioid initiation

Of the 1,749,897 adult patients prescribed with oral and transdermal opioid prescriptions between January 2000 and December 2015, 1,021,885 (58.4%) were eligible to link their CPRD data with ONS death certification; of which, 902,149 (88.3%) were followed more than one year from opioid initiation to follow-up endpoint and included as the study cohort. The mean of follow-up duration from opioid initiation was 7.9±5.8 years (range: 1 to 25 years).

Of the study cohort, 369,548 (41.0%) of them were male. The median age of the study cohort at opioid initiation was 52 years (interquartile range: 38, 66). There were 59,956 (6.7%) individuals diagnosed with cancer before opioid initiation. In the one year before opioid initiation, there were 25,030 (2.8%) and 3,550 (0.39%) opioid users diagnosed with alcohol and other substance abuse disorders. About 28% (n=256,107) of the study cohort had records of chronic pain, and low back pain was the most common diagnosis (n=206,284, 22.9%). There

were 65,005 (7.2%) opioid users with a record of any psychological illnesses or psychological consultations, and 52,778 (5.9%) and 20,032 (2.2%) opioid users had records of depression and anxiety in the one year before opioid initiation (Table 24).

Table 24. Baseline characteristics of study cohort

Characteristics	Category	Study cohort (n=902,149)
Gender	Male	369,548 (41.0%)
Mean age	Mean ± standard deviation (years)	52.1±18.1
Age rank	18≤age<40 years	252,111 (28.0%)
	40≤age<65 years	403,446 (44.7%)
	65≤age<80 years	183,285 (20.3%)
	80 years ≤age	63,307 (7.0%)
Townsend score	1	180,867 (20.1%)
	2	189,920 (21.1%)
	3	189,600 (21.0%)
	4	193,816 (21.5%)
	5	147,254 (16.3%)
Substance abuse disorder	Alcohol	25,030 (2.8%)
	Other substance	3,550 (0.39%)
Chronic pain	Any chronic pain	256,107 (28.4%)
	Low back pain	206,284 (22.9%)
	Arthritis	53,335 (5.9%)
	Neuropathic pain	4,017 (0.45%)
	Fibromyalgia	1,933 (0.21%)
Other pain conditions	Abdominal pain	61,199 (6.8%)
	Headache	52,688 (5.8%)
	Migraine	17,731 (2.0%)
	Pelvic pain	5,358 (0.59%)
	Post-operative pain	2,154 (0.24%)
	Pancreatitis	1,454 (0.16%)
	Kidney stone	687 (0.08%)
Psychological illnesses	Any psychological illnesses	65,005 (7.2%)
	Depression	52,778 (5.9%)
	Anxiety	20,032 (2.2%)
	Sleep disorder	23,041 (2.6%)
	Panic	4,500 (0.5%)
	Post-traumatic stress disorder	744 (0.08%)
	Schizophrenia	360 (0.04)
Cancer		59,956 (6.7%)

(Note) Number and proportion of patients in study cohort were presented

Townsend score: A index of material deprivation and disadvantage measured by four dimensions, including unemployment, car ownership, home ownership and household overcrowding.

8.4.2. Balanced characteristics between cases and controls

Overall, 232 opioid-related deaths were identified from the 902,149 study cohort. Of these, 230 opioid-related deaths were matched to 920 controls from adult opioid users at risk when opioid-related deaths occurred; 2 opioid-related fatalities did not match to any adult opioid users by disease risk score, and hence in total 1150 patients were included in the analysis. The demographic characteristics, psychological illnesses and pain conditions were balanced well between cases of opioid-related deaths and their matched controls on the index date (Table 25).

Table 25. Balance of patient characteristics and disease conditions in one year before index date between cases of opioid-related deaths and their matched controls

Characteristics		Case (n=230)	Matched controls (n=920)	p-value
Gender	Male	123 (53.5%)	496 (53.9%)	0.906
Age (years)	Mean ± standard deviation	50.1±14.1	49.1±14.3	0.3265
	18≤age<40	51 (22.2%)	253 (27.5%)	0.293
	40≤age<65	139 (60.4%)	533 (57.9%)	
	65≤age<80	28 (12.2%)	104 (11.3%)	
	80 ≤age	12 (5.2%)	30 (3.3%)	
Townsend score	1	15 (6.5%)	46 (5%)	0.298
	2	23 (10%)	119 (12.9%)	
	3	47 (20.5%)	162 (17.6%)	
	4	84 (36.5%)	305 (33.2%)	
	5	61 (26.5%)	288 (31.3%)	
Cancer	Yes	23 (10%)	73 (7.9%)	0.311
Medication review	Yes	102 (44.4%)	386 (42%)	0.512
Overdose	Yes	18 (7.8%)	65 (7.1%)	0.690
Substance abuse disorder	Alcohol	20 (8.7%)	86 (9.4%)	0.760
	Other substance	13 (5.7%)	43 (4.7%)	0.538
Chronic pain	Any	45 (19.6%)	175 (19%)	0.851
	Low back pain	38 (16.5%)	164 (17.8%)	0.642
	Arthritis	4 (1.7%)	8 (0.87%)	0.246
	Neuropathic pain	3 (1.3%)	11 (1.2%)	0.893
	Fibromyalgia	2 (0.87%)	4 (0.43%)	0.413
Other pain conditions	Any complaint about pain	60 (26.1%)	273 (29.7%)	0.283
	Surgical pain	30 (13%)	107 (11.6%)	0.554
	Abdominal pain	26 (11.3%)	96 (10.4%)	0.702
	Headache	10 (4.4%)	39 (4.2%)	0.942
	Pancreatitis	4 (1.7%)	8 (0.87%)	0.246
	Migraine	2 (0.87%)	10 (1.1%)	0.772
	Kidney stone	1 (0.43%)	6 (0.65%)	0.705
	Post-operative pain	1 (0.43%)	5 (0.54%)	0.838

(Note) Number and proportion of patients in case and control groups were presented.

Table 25. Balance of patient characteristics and disease conditions in one year before index date between cases of opioid-related deaths and their matched controls (continued)

Characteristics		Case (n=230)	Matched controls (n=920)	p-value
Psychological illnesses	Depression	33 (14.4%)	153 (16.6%)	0.400
	Sleep disorder	18 (7.8%)	53 (5.8%)	0.244
	Anxiety	16 (7%)	88 (9.5%)	0.217
	Panic	2 (0.87%)	11 (1.2%)	0.676
Cardiovascular	Any cardiovascular disease	49 (21.3%)	185 (20.1%)	0.687
	Hypertension	4 (1.7%)	26 (2.8%)	0.355
	Diabetes	17 (7.4%)	75 (8.2%)	0.704
Respiratory disease	Asthma	37 (16.1%)	122 (13.3%)	0.267
	Upper Respiratory Infection	28 (12.2%)	112 (12.2%)	0.999
	Shortness of breath	4 (1.7%)	17 (1.9%)	0.912

(Note) Number and proportion of patients in case and control groups were presented.

Townsend score: An index of material deprivation and disadvantage measured by four dimensions, including unemployment, car ownership, home ownership and household overcrowding.

8.4.3. Persistent opioid utilisation

Of the 1150 matched cases and controls, 373 (32.4%) patients ever used opioid persistently from opioid initiation. Of whom, 272 (72.9%) and 341 (91.4%) of them ever used opioid persistently in the first patient-year and one of the three retrospective follow-up patient-year. The proportion

of persistent opioid users defined as the wide definition group was higher in the case group than the control group in the first (43.5% vs 18.7%, p<0.001) and up to the third retrospective patient-year (55.7% vs 23.2%, p<0.001). Higher proportions of opioid users in the case group were categorised as persistent opioid users by strict definition when compared to control group in the first (24.3% vs 7.5%, p<0.001) and up to the third retrospective patient-year (30.4% vs 8.2%, p<0.001). Regarding the pattern of persistent opioid utilisation, a higher proportion of opioid users in the case group were categorised into each pattern of persistent opioid utilisation during the three retrospective patient-years (Table 26).

Table 26. Proportion of persistent opioid users in cases and controls groups during the first and up to the third retrospective patient-year

	First retrospective patient-year*		One of the three retrospective patient-year*	
	Case	Control	Case	Control
Persistent opioid utilisation				
Wide	100 (43.5%)	172 (18.7%)	128 (55.7%)	213 (23.2%)
Intermediate	80 (34.8%)	117 (12.7%)	98 (42.6%)	139 (15.1%)
Strict	56 (24.4%)	69 (7.5%)	70 (30.4%)	75 (8.2%)
Pattern of persistent opioid utilisation				
In the second or third but not in the first patient-year			46 (20%)	93 (10.1%)
In the first patient-year			19 (8.3%)	33 (3.6%)
In all of the three patient-years			63 (27.4%)	87 (9.5%)

(Note) * all p-value < 0.001

8.4.4. Association between opioid-related deaths and persistent opioid utilisation in the first retrospective patient-years

In the first retrospective patient-year, compared to patients who were not prescribed with opioids persistently, persistent opioid users did not have a higher risk of opioid-related deaths (aOR: 1.3, 95%CI: 0.81, 2.0) after adjusting for the prescriptions of concurrent sedatives. However, patients who were concurrently prescribed antipsychotics (aOR: 2.3, 95%CI: 1.2 to 4.4) and non-gabapentin/pregabalin anticonvulsants (aOR:

3.0, 95%CI: 1.1 to 7.8) in the first retrospective patient-year had a significantly higher risk of opioid-related deaths.

In addition, patients who were prescribed mean daily dose of gabapentin/pregabalin for more than 1 DDD (aOR: 5.4, 95%CI: 2.4 to 12.1) and TCAs for more than 0.5 DDD (aOR: 2.6, 95%CI: 1.4 to 4.7) concurrently with opioids had a significantly increased risk of opioid-related deaths. Furthermore, patients who were concurrently prescribed with either medium (less than 1 DDD) or higher (more than 1 DDD) mean daily dose of BZDs with opioids had a significantly higher risk of opioid-related deaths with the aOR of 3.4 (95%CI: 1.8, 6.4) and 7.7 (95%CI: 4.3, 13.8), respectively (Table 27).

Table 27. The association between persistent opioid utilisation and opioid-related deaths after adjusting for concurrent sedatives in the first retrospective patient-year

Medicine utilisation	Category	aOR (95%CI)	p-value
Persistent opioid utilisation	No	1 (reference)	0.2839
	Yes	1.3 (0.81, 2.0)	
Use of antipsychotics	No	1 (reference)	0.0093*
	Yes	2.3 (1.2, 4.4)	
Use of non-gabapentin/ pregabalin anticonvulsants	No	1 (reference)	0.0251*
	Yes	3.0 (1.1, 7.8)	
Benzodiazepine	0 DDD	1 (reference)	<0.0001*
	0< to ≤1 DDD	3.4 (1.8, 6.4)	
	>1 DDD	7.7 (4.3, 13.8)	
Gabapentin/ pregabalin	0 DDD	1 (reference)	0.0001*
	0< to ≤1 DDD	1.8 (0.93, 3.4)	
	>1 DDD	5.4 (2.4, 12.1)	
Tricyclic antidepressants	0 DDD	1 (reference)	0.0045*
	0< to ≤0.5 DDD	0.92 (0.46, 1.8)	
	>0.5 DDD	2.6 (1.4, 4.7)	

(Note) DDD: defined daily dose, aOR: adjusted odds ratio ; * p<0.05

8.4.5. Association between different patterns of persistent opioid utilisation and opioid-related death

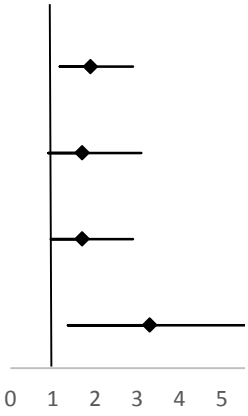
Compared with non-persistent opioid users, patients identified as persistent opioid users in any of the three patient-years (aOR: 1.9, 95%CI: 1.2 to 2.9) had an increased risk of opioid-related death after

adjusting for concurrent sedatives (Appendix 10). However, a non-significant increase in the risk of opioid-related deaths was found for the pattern that persistent opioid utilisation in all the three patient-years (aOR: 1.7, 95%CI: 0.94 to 3.1) (Appendix 11).

Compared with non-persistent opioid users, a significant but marginal increase in the risk of opioid-related deaths was found for persistent opioid utilisation in the second or third but not in the first retrospective patient-year (aOR: 1.7, 95%CI: 1.0 to 2.9) (Appendix 12). Also, persistent opioid utilisation in the first patient-year was associated with the highest odds of opioid-related deaths (aOR: 3.3, 95%CI: 1.5 to 7.4) (Appendix 13) when compared to non-persistent opioid users in the three patient-years (Table 28).

Table 28. Summary of the association between opioid-related death and different patterns of persistent opioid utilisation in the three retrospective patient-years

The pattern of persistent opioid utilisation	Odds ratio (95%CI)
Persistent opioid utilisation in any of the three patient-years	1.9 (1.2, 2.9)
Persistent opioid utilisation in all the three patient-years	1.7 (0.94, 3.1)
Persistent opioid utilisation in the second or third but not in the first patient-year	1.7 (1.0, 2.9)
Persistent opioid utilisation in the first patient-year	3.3 (1.5, 7.4)



(Note) After adjusting the use of BZDs, gabapentin/ pregabalin, antipsychotics and TCA.

8.5. Discussion

8.5.1. Main findings

Persistent opioid utilisation in the first retrospective patient-year before death was not associated with opioid-related death. Once considering the pattern of persistent opioid utilisation up to three patient-years, persistent opioid utilisation in all the three patient-years was not associated with an increased risk of opioid-related deaths, but persistent opioid utilisation in any patient-year was associated with an increased risk of opioid-related death.

In particular, persistent opioid utilisation in the first year before death was at the highest risk of opioid-related death when compared to non-persistent opioid users in the three patient-year. The increased risk of opioid-related death for persistent opioid utilisation in any one of the three-retrospective patient-years implies a long-term effect of persistent opioid utilisation and history of opioid prescriptions should be considered.

In addition to persistent opioid utilisation, the use of BZDs, gabapentin/pregabalin, antipsychotics and TCAs was consistently associated with opioid-related death and taking a higher dose of BZDs, gabapentin/pregabalin and TCAs were associated with a higher risk of opioid-related death.

8.5.2. Association between opioid-related deaths and persistent opioid utilisation in any patient-yea

The results of this study indicate that a history of persistent opioid utilisation should be considered in assessing the association between opioid-related deaths and persistent opioid utilisation in the UK. Nevertheless, this is the first study worldwide evaluating the association between persistent opioid utilisation and opioid-related death, and hence the results of this study are not directly comparable to previous publications.

In North America, opioid-related harm is considered mainly relating to

opioid overdose. Only a few studies identified chronic opioid users as the study cohort and evaluating opioid overdose death or drug overdose in relation to opioid daily dose[9, 132, 277]. According to the SR conducted by the CDC, all epidemiology studies conducted in North America quantified the relative risk of opioid-overdose deaths for patients prescribed with high opioid daily dose rather than persistent opioid utilisation[19].

The history of persistent opioid utilisation in previous patient years might explain the non-significant association between opioid-related deaths and persistent opioid utilisation in the first patient year when only considering one-year opioid prescriptions. From opioid initiation to the index date, there were only about 70% of all persistent opioid users were prescribed opioids persistently in the first retrospective patient-year, and thus implied that 30% of patients who ever used opioids persistently from opioid initiation were categorised as non-persistent opioid users in the first retrospective patient-year.

As persistent opioid utilisation in any of the three patient years was associated with opioid-related death, the history of persistent opioid utilisation in other patient years induced a non-differential misclassification error due to the observed period to quantify persistent opioid utilisation and tend to a non-significant difference between study groups once only opioid prescriptions in the first patient year been considered[281, 282]. Therefore, these results imply that opioid prescriptions in a longer period of time rather than only in the first patient year should be considered when evaluated the association between opioid-related deaths and persistent opioid utilisation.

8.5.3. A higher dose of opioids received by persistent opioid users identified in the first retrospective patient year

The interaction between the mechanism of opioid tolerance, increasing opioid prescribing and fatal opioid overdose could potentially explain the greatest risk of opioid-related deaths found in the first patient year once

considered opioid prescriptions in the three patient years.

Mellbye *et al.* (2015) found that more than 60% of persistent users at the sixth patient-year also used opioids persistently in one of the previous years, which is consistent with the results in a previous cohort study (Section 4.4.4, Page 132). Due to opioid tolerance which means a higher dose is required to achieve the original response, Mellbye *et al.* found that more than 65% of persistent opioid users who remained in persistent opioid utilisation up to the sixth patient years had increased their annual opioid dose at least 25% when comparing to the dose in the first patient-year[40].

According to a SR of RCTs exploring the efficacy of interventions on opioid dose tapering, no intervention showed a significant difference in reducing opioid dose between study groups[300]. Especially, more severe withdrawal symptoms and longer duration to taper opioid dose were found for patients taking opioid for larger daily dose or longer period of

time[301].

Therefore, due to the tendency of increasing opioid dose associated with opioid tolerance and the difficulty in reducing the opioid dose, persistent opioid users in the first patient year would receive a relative higher opioid dose. As opioid-related serious adverse effects, such as respiratory depression are dose-depenent[48], greatest risk of opioid-related deaths was expected for persistent opioid utilisation in the first patient-year.

8.5.4. Association between opioid-related deaths and different patterns of persistent opioid utilisation

For opioid-related deaths who ever received opiate substitution treatment in England and Wales, more than 80% of them with opioid-related death occurred when leaving substitution treatment[302]. For patients who ever received opioid substitution treatment, relapse to opioid use was found associated with opioid-related death as the

tolerance to opioids decreased during treatment abstinent and original dose would be too high once patients and physician were unaware about the decreased tolerance[303, 304]. In addition, higher risk of opioid-related deaths was also found during the induction on opiate substitution treatment once physician did not aware non-prescribed opiate and initiate with high dose methadone[305].

Physicians or patients unawareness of the change in opioid tolerance might also be relevant to the association between opioid-related deaths and persistent opioid utilisation in the second and third patient-year. Due to the nature of pain, patients would re-initiate analgesics even their current pain conditions have been relieved and analgesics have been discontinued[39, 40]. However, for patients who ever been persistent opioid users, they might take remain opioids with the original dose from their previous prescriptions to achieve pain relief. Once patient unawareness of the change in opioid tolerance, high dose of opioids increased the risk of opioid-related deaths, and this mechanism also explained there were

more than one-quarter of opioid-related deaths who were not prescribed with any opioid in the final year before death (Section 7.4.3, Page 251).

Close monitoring such as daily dispensing and supervision of methadone dosing has been suggested to decrease opioid-related deaths among patients with opiate substitution treatment in England and Wales[28, 135]. Comparing to patients switching between persistent and non-persistent opioid utilisation, patients remaining in persistent opioid utilisation might imply more regular clinic visits and dose monitor, and hence patients with persistent opioid utilisation in all of the three patient-years were less likely to suffer opioid-related deaths. Not only patients with opiate substitution treatment, these results imply the concept that close monitoring might also decrease the risk of opioid-related death among persistent opioid users.

8.5.5. Concurrent sedatives and the association between opioid-related deaths and different patterns of persistent opioid utilisation

The benefits and risks of the combination of opioids and sedatives for pain control and psychological illnesses need further evaluation. Medicines for depression, anxiety and insomnia are often indicated for patients with persistent pain[10-12]. However, most of the RCTs exploring the efficacy of long-term opioid utilisation were less than three months in duration and evaluated the efficacy of opioid alone rather than the combination of opioid and sedatives, and hence the efficacy of the long-term concurrent use of opioid and sedatives was still unclear.

Furthermore, the combination use of opioids and a higher daily dose of BZDs has been associated with an increased risk of opioid-overdose death in the US[43, 289], and current prescribing guidance in the US recommends physicians should avoid concurrent use of BZDs and opioids[19]. In addition, a published nested case-control study conducted

by Gome *et al.* (2017) in Canada showed an increased risk of opioid-overdose death among patients prescribed a combination of opioid and high doses of gabapentin/pregabalin, which is consistent with the result from this study[44]. In addition to BZDs and gabapentin/ pregabalin, our study also found a consistent significant association between opioid-related death and concurrent use of antipsychotics and TCAs.

However, the association estimated from this study was influenced by other significant factors, such as persistent opioid utilisation. As current prescribing guidance in the UK only suggested avoiding the combination of opioids and BZDs, further studies should evaluate the association between opioid-related deaths and concurrent gabapentin/ pregabalin, antipsychotics and TCAs after controlling for potential confounding factors.

8.5.6. Strengths and limitations

This is the first nested case-control study to evaluate the association

between opioid-related deaths and persistent opioid utilisation in the UK general practice. Although a case-cohort study design may identify potential determinants of rare adverse events, this study design explored factors associated with outcomes of interest (opioid-related death) by performing analysis as a cohort study in a cohort which included cases of event (opioid-related deaths) and an additional group of patients randomly selected from the same target cohort (opioid users), and hence the estimated association was influenced by other confounding factors[306]. Compared with case-cohort study design, this study applied nested case-control study design to evaluate the association between the exposure of interest (persistent opioid utilisation) and rare adverse events by eliminating potential confounding factors in the matching process.

Regarding the selection of study cohort, compared to studies which evaluated the risk of opioid-overdose death but only included patients with socioeconomically disadvantaged and less than 65 years in

Canada[42, 44], this study selected opioid users from electronic healthcare records (CPRD) which is representative to age and gender distribution in the UK and did not exclude elderly patients. Therefore, the results could be better generalised to the ageing cohort of opioid-related deaths in the UK[25].

Comparing to the majority of case-control studies which apply a limited number of variables in the matching process (quite often less than three, including age, gender and index date) and imbalance in variables which were not involved in matching process was often found[307], this study used a disease risk score summarising the probability of opioid-related deaths and a balance in multiple confounding factors between case and control group was achieved by the matching process.

In addition, comparing to a published nested case-control study which included age and gender in both the calculation of disease risk score and matching process and hence led to an imbalance in alcohol abuse

between opioid-overdose death and matched controls[42], a balance was achieved between cases of opioid-related deaths and matched controls in all characteristics involved in disease score calculation in this study.

There are some limitations to this study. Firstly, only opioid users (58.4%) registered in a proportion of practices in England and Wales are linkage eligible to the ONS death certification and 54 of the 286 opioid-related deaths (18.9%) using opioids for less than one year were excluded from this study. Therefore, the results from this study may not be generalizable to Scotland and North Ireland and cannot be applied to patients who used opioids less than one year. Secondly, most characteristics used in disease risk score calculation such as substance abuse are chronic conditions but not included in Quality and Outcomes Framework Indicators[308], and potential missing data would cause underestimation of these characteristics.

8.6. Conclusion

In conclusion, a history of persistent opioid utilisation defined by a MDA

and concurrent use of sedatives and opioids were associated with opioid-related deaths. In clinical practice, healthcare providers in the UK need to be aware of the history of persistent opioid utilisation even patients were not persistent opioid users at the moment. Further studies should explore the safety and effectiveness of concurrent opioids and sedatives and adjust for potential confounding factors in order to inform further development of evidence-based prescribing guidance.

Chapter 9. Discussion and conclusion

9.1. Main findings

This study adopted a drug utilisation research and pharmacoepidemiology approach to develop and test a hypothesis about the association between opioid utilisation and opioid-related deaths in the UK and applied tramadol as a case study to evaluate the impact of regulatory change on tramadol utilisation and tramadol-related deaths. The results of this study advance the knowledge in understanding the reasons for increasing opioid utilisation, the challenges of inferring the association between opioid utilisation and opioid-related harms, and the effectiveness of policy on limiting opioid accessibility and reducing opioid-related deaths in the UK.

This study was initially motivated by the change in controlled drug policy for tramadol prescribing in England and Wales corresponding to increasing tramadol utilisation which was related to increasing prevalence of tramadol users, recurrent use and prolonged use of

tramadol for CNCP and the association between increasing tramadol utilisation and the rising number of tramadol-related deaths. The result of this study found that after tramadol classification, the prescribing of tramadol decreased; furthermore, the number of tramadol-related deaths also decreased. The effectiveness of tramadol classification seems predominantly related to reduced accessibility of tramadol to both new and existing tramadol users (Chapter 3). As the recurrent use and prolonged use of tramadol caused an increasing trend in tramadol utilisation and tramadol-related deaths, this study assumed that persistent tramadol utilisation was one of the determinants associated with tramadol-related deaths in the UK.

Currently, there is no gold standard to measure persistent utilisation of singe opioid or opioids as a class. Assuming that persistent opioid use is mainly for patients with chronic pain which is often intermittent and recurrent, and hence dose, duration and frequency of opioid prescribing should be considered for measuring the persistence. To study the

persistent utilisation of tramadol, a MDA which considers possible dimensions of persistence was applied in this study[39], and the results showed that about 20% of users were prescribed with tramadol persistently (Chapter 4).

The result indicated that use of the MDA which was initially designed to assess the persistence of opioids as a class is feasible to identify persistent tramadol utilisation that may potentially lead to serious adverse events, including tramadol-related deaths. However, tramadol-related deaths are attributed to a complex mechanism which is not simply explained by the persistent exposure of tramadol. Instead, other confounders need to be considered in the pharmacoepidemiological study design to evaluate the causality between tramadol utilisation and serious adverse events.

For example, opioid analgesics share similar pharmacological mechanism which may cause serious side effects, such as respiratory

depression; hence they should be considered as the same class of exposure to infer their associated outcomes (such as deaths). In fact, this study found that tramadol users were often prescribed with other medications which were potentially associated with serious adverse events. For example, about 10% and 20% of tramadol users were prescribed antidepressants and BZDs before tramadol initiation. In addition, non-persistent tramadol users also received other opioids and had a higher annual number of supply days and mean opioid daily dose than persistent tramadol users (Chapter 5). Besides, persistent opioid users were more often to concurrently be prescribed opioids with sedatives during the periods of opioid therapy, and the higher mean daily dose of concurrent sedatives was found when compared to non-persistent opioid users (Chapter 5).

Moreover, in this study, tramadol-related deaths cannot be differentiated from the opioid-related death according to the records of the ONS death certificate. Therefore, instead of studying the tramadol-related death, the

focus of this study was re-directed to evaluate the association between utilisation of prescribing opioids and opioid-related deaths and considered the concurrent uses of sedatives which may also lead to drug-misuse mortality. Nevertheless, the definition of opioid-related death in the UK is different from opioid-overdose death in the US, which is mainly related to opioid poisoning, and the published method from the UK ONS included all opioids, and hence methadone-related deaths which were mainly related to the implementation of opioid substitute treatment cannot be differentiated. It is necessary to consider the feasibility of applying official registry data (ONS death certificate) and revised methods to define opioid-related deaths (Chapter 6) and further understand the characteristics of opioid-related deaths before inferring the causality with opioid exposure, in particular, persistent opioid utilisation.

Subsequently, a case review of opioid-related deaths in the UK was conducted, and the results showed that opioid-related deaths were not

necessarily associated with high opioid doses, as the majority of cases of opioid-related deaths in the UK received opioids with long duration but low daily dose; and about a quarter of them were not prescribed any opioid in the final year before death. In addition, most opioid-related deaths were regularly prescribed sedatives and diagnosed with alcohol or substance abuse disorder, psychological illnesses, or had a history of overdose of any medication. In fact, no significant association was found between opioid daily dose more than 120 mg OMEQ per day and opioid-related death when considering other sedatives (Chapter 7).

Therefore, instead of high-dose exposure of opioids, it was assumed that persistent use of opioids or concurrent use of other sedatives is the main reason of opioid-related deaths in the UK. Therefore, the association between persistent opioid utilisation and opioid-related death was explored in a nested case-control study, and the results found that persistent opioid utilisation was significantly associated with opioid-related death especially persistent opioid utilisation in the final

year was associated with the highest risk of opioid-related death when compared to non-persistent opioid users (Chapter 8).

9.2. Strengths and limitations of this study

This study applied a pharmacoepidemiology approach which included quantifying opioid utilisation for hypothesis building, identifying confounding factors and testing the association between persistent opioid utilisation and opioid-related deaths. The association between opioid utilisation and opioid-related death was also progressively tested using aggregate level and individual-patient level data. In addition, this study used big data sources to increase generalizability and linked multiple data sources to identify potential confounding factors and examine measurement error following the suggestions from the US CDC and the review conducted by Ranapurwala *et al.* (2018)[19, 133].

The applied aggregate-level prescribing data coved all practices in

England, and the CPRD and linked ONS death certification included 8% of UK population and all cases of opioid-related deaths and hence were highly represented in the UK. Furthermore, different study designs were used to measure utilisation of opioids and sedatives and identify the association between opioid utilisation and opioid-related deaths based on different purpose and hypothesis leading to opioid-related deaths.

However, there were some limitations to this study that are attributed to the natural limitations of using secondary databases for pharmacoepidemiology studies. Although CPRD is the most extensive healthcare records in the UK and the official registry (ONS death certification) covered all opioid-related deaths in England and Wales, only part of practices consented to link registrants' information in the CPRD with ONS death certificate; and hence the number of cases included in this study is not the total number of opioid-related deaths in England and Wales. Moreover, since there were variations in registrants' characteristics among practices in the UK, it is likely that the included

cases might not be fully represented in the distribution of comorbidities of all opioid-related deaths[309-312].

Also, the influence of unmeasured confounders such as pain intensity and opioid tolerability cannot be quantified as that information was not necessarily recorded in the primary care system, and thus may impact on the estimate of disease risk score for predicting the probability of opioid-related deaths and bias the selection of matched controls. The diagnosis of substance abuse and other pain conditions recorded in the UK primary care database are not widely validated in the UK, and hence potential misclassification of patients' characteristics may have occurred.

As this study identified medicine exposure, including daily dose, persistent utilisation and concurrent sedatives from primary care prescription records, it was assumed that patients take medications exactly as prescribed. Furthermore, patients might be referred to

secondary care or emergency department for managing acute or severe pain or other medical conditions, or be referred to the Addition Treatment Centres for managing substance misuse, and medicines prescribed in those settings are not recorded in the CPRD[189, 190]. Therefore, it was also assumed that opioids prescribed in the secondary care are mainly for short-term conditions such as acute pain; hence the impact on any persistence measure is limited. These assumptions need to be further validated in the future. Moreover, information about the over-the-counter, diversion and illicit use of medicines are also not available.

Another challenge in assessing the opioid-related deaths in the UK is the lack of information on the specific outcome measure. The original purpose of monitoring opioid-related mortality in the UK initiated from concerns regarding drug-misuse deaths[28]. The official definition of opioid-related deaths was a subset of drug-misuse deaths which include deaths related to methadone; furthermore, the current post-mortem test in England and Wales cannot differentiate deaths which occurred as a

result of the use of heroin and morphine because heroin was metabolized into morphine in human body[28]. Consequently, the operational definition published by the ONS to identify opioid-related deaths also include deaths which occurred as a result of using other substances or illicit drugs which are not prescribed for pain control, such as heroin and methadone. Therefore, in this study, the feasibility of several operational definitions was identified by describing the trend of opioid-related deaths and the distribution of characteristics when compared to official statistics.

The limitations of using secondary healthcare data sources to infer the causality between opioid utilisation and its associated deaths are commonly found in existing literature. In the US, the most frequently reported opioids involving in opioid-overdose deaths are prescribed opioids[128, 129]. Although studies identifying the association between opioid-overdose death and opioid daily dose used a variety of data from outpatient dispensing records of single health plan[7], dispensing records

of single health plan[9, 84], state-wide outpatients dispensing records[41] or dispensing records of public benefit program[42], they still did not include information of opioid consumption from all possible routes. The measurement error on opioid prescriptions in studies evaluating the association between prescribing opioids and opioid-related harm[19] has been highlighted in the US CDC guideline and requires different approaches to retrieve the information.

The misclassification of opioid-related mortality is also a challenging issue. Instead of applying the ICD-10 diagnosis codes in medical records, Roxburgh *et al*. (2018) applied various sources of information, including demographics, cause of death, and associated documentation on toxicology, clinical and police investigations (such as the evidence of intravenous drug use) to identify and differentiate opioid-overdose deaths involving different opioids in the National Coronial Information System (NCIS) in Australia. The results found that about a quarter of morphine-related deaths were recorded to heroin-related deaths after

the NCIS's investigation[313].

Although Roxburgh *et al*. demonstrated the feasibility of applying toxicology, clinical and police investigations to differentiate deaths involving different opioids, that information is not available in the linked ONS death certificate used in this study. Understanding the risk associated with opioids from prescribing or non-prescribing routes to differentiate opioid-related deaths involving illicit and non-illicit opioids will help to better inform policy and clinical practice.

In contrast to published studies which applied 'prescription gap', 'number of prescriptions' and 'number of days' to identify persistent opioid users and investigate the safety associated with opioid utilisation[8, 9, 206], this study defined and measured 'persistent opioid utilisation' in each patient-year. Therefore, to infer the causality in the nested case-control study, included patients required to have more than one-year follow-up duration (Section 8.3.1, Page 281). In addition, in order to evaluate the

association between opioid daily dose and opioid-related death within the same patients using a case cross-over study design (Section 7.3.2, Page 239), cases of opioid-related death were required to have more than one-year follow-up duration and hence raised the concern of potential immortal time bias.

Immortal time means a period in which the events could not occur because of the definition of exposure[314]. Among opioid-related deaths identified from the linkage ONS death certificate, about 20% were either registered less than one year in CPRD after opioid initiation or transferred out from the CPRD before opioid-related death occurred. Therefore, excluding those patients might potentially contribute to the non-significant association between opioid-related deaths and opioid daily dose.

9.3. Strategies for optimising opioid utilisation

Although the evidence for inferring the causality between prescription opioid utilisation and opioid-related death in the UK still needs further investigation, the evidence raises a signal that the improving prescribing of opioids and other sedatives (e.g. antidepressants and anticonvulsants) is an urgent public health issue. Globally, to control increasing opioid prescribing and to prevent opioid-related mortality and harms, many policy and strategies have been implemented.

Approaches for improving and optimising the quality and efficiency of prescribing can be categorised by ‘supply-side’ measures and ‘demand-side’ measures. ‘Supply-side’ measures aim to reduce the price of medicines and include mandatory price cuts, reference pricing in a class and delisting of products from reimbursement. ‘Demand-side’ measures aim to control increasing medication prescribing by influencing physicians’ behaviour and can be categorised under the ‘4E’ approach, including education, engineering, economics and

enforcement measures[315].

In general, education measures are strategies that influenced prescribing by educational materials and activities. Engineering measures include those influencing prescribing through managerial or organisational intervention[315, 316]. Economics measures include financial interventions, such as incentives and penalties for physicians, pharmacists and patients. Enforcement measures refer to regulations that limit prescribing[315, 317].

The strategies commonly applied to optimise the use of opioids include regulation change, pharmacovigilance systems, prescribing guidance and deprescribing by healthcare service. These strategies cover different measures in the 4E approach, and hence have individual strengths and limitations to control increasing opioid prescribing and opioid-related harms.

9.3.1. Limit accessibility to controlled medicines – the central decision-making level

To control increasing utilisation by limiting the accessibility, drug regulation is related to enforcement measures of the 4E approach, and these compulsory measures have been regarded as easier to implement than other measures[315]. Enforcement measures regulate the availability of medicines or their prescribing by positive lists or population restrictions, but it might not be effective in changing physicians' behaviour as physicians could still prescribe other medications to replace the original medications and limit the effectiveness of enforcement measures[318].

The WHO policy guidance on controlled substance, which aims to support government representatives and policymakers in assessing their legislation, suggests that the controlled drug regulation should balance the benefits and risks of controlled substances among general

population[319]. Although the majority of countries list opioids as controlled substances, there is variation in the national legislation and regulation about opioid prescribing between countries, such as the limitation in prescription duration[320-322].

In this study, tramadol utilisation was measured at an aggregate-level for the time-series analysis and results showed the launch of tramadol classification decreased the number of both new and existing tramadol users, and reduced the increasing utilisation of tramadol and tramadol-related deaths in England and Wales (Chapter 3). It is possible that limiting the accessibility of tramadol reduced unnecessary and unsafe prescribing, such as people who misuse tramadol and hence decreased tramadol-related death. However, despite the effectiveness of tramadol classification, the impacts of regulation on persistent tramadol utilisation and hence leading to decreasing tramadol-related death is still unclear as this study described tramadol utilisation at an aggregate-level rather than individual patient level.

In addition, studies have shown that changing the classification of opioids or withdrawing them from the market has impacts on the availability and prescribing of opioids[183-185]. However, it does not solve the fundamental issues about the unmet needs of patients with chronic pain and substance abuse, and it was also reported that physicians substantively prescribed other medicines in the same pharmacological class instead in order to achieve adequate pain relief [183-185]. Consequently, the increased prescribing of other opioids or medications with abuse potential was found[323]. For example, in the US, after the re-scheduling of hydrocodone/acetaminophen combination in October 2014, the number of non-combined hydrocodone, tramadol and codeine prescriptions increased[184, 185].

In the UK, prolonged opioid prescribing for CNCP has been considered as one of the main reasons for increasing opioid utilisation[29, 87]. In recent years, co-proxamol was withdrawn from the market and tramadol was

classified as a controlled medicine due to increasing opioid-related deaths and co-proxamol and tramadol use disorder[33, 177]. The previous study found that dispensed codeine preparations increased after withdrew of co-proxamol in England and Wales in January 2005[183]. In this study, a time-series analysis was also conducted to evaluate the impacts of tramadol classification on the utilisation trend of other opioid analgesics, and the results found that the level and trend of the number of DDDs per 1000 registrants per month of other opioids did not change after tramadol classification in England and Wales[324].

Although there is no evidence of substitution between tramadol and other opioids in a short-term after tramadol classification, it is still possible that the policy may affect medications with other pharmacological effects which are also indicated for pain control, such as antidepressants and anticonvulsants. In addition, patients with substance use disorders are considered to have a higher risk for developing abuse or addiction with multiple substances[325, 326]; therefore,

limiting the accessibility of single opioid might not be useful for controlling overall drug-related harm. It is reasonable to hypothesise that patients with tramadol use disorder might switch to other prescribed substances once the accessibility of tramadol was regulated.

After withdrawal of co-proxamol in the UK, pregabalin and gabapentin prescribing has increased by 350% and 150% from 2007 to 2013[323], and the number of drug-related deaths involving pregabalin and gabapentin also increased from 12 in 2012 to 165 in 2016 after tramadol classification in 2014 in England and Wales[234]. Although the increasing deaths and utilisation of pregabalin and gabapentin might not be entirely attributed to the withdrew of co-proxamol and the classification of tramadol, there are increasing publications about the concerns of pregabalin and gabapentin abuse[327, 328] especially almost all drug-misuse deaths related to pregabalin and gabapentin involving multiple substances and more than 80% of drug-misuse deaths related to pregabalin and gabapentin involving opioids[329].

The age-adjusted drug-related mortality increased from 2.8 cases per 100,000 inhabitants between 2003 and 2005 to 4.2 cases per 100,000 inhabitants between 2014 and 2016 in England[234]. After tramadol classification, the overall number of both drug-misuse deaths and opioid-related deaths still increased in 2015 and 2016. Concerning the potential risk of abuse and growing number of deaths, pregabalin and gabapentin were recommended to be classified as Class C Control Substances by the ACMD in January 2016[330]. Although this decision was under public consultation between November 2017 and January 2018 and the final decision is still awaited at the time of completing this thesis, further research is needed to evaluate the effect on drug-misuse death once pregabalin and gabapentin were classified as control substances.

9.3.2. Prescribing indicators and registry monitoring – the signal detection and risk management system

In addition to limiting opioid accessibility at the central decision-making level, some countries also have implemented pharmacovigilance approaches to monitor potential problematic use of opioids, for example, the PDMPs in the US, registry of Review and Approval Committee on Controlled Drugs for Medical Use (RACCDMU) in Taiwan, and the Campaign to Reduce Opioid Prescribing (CROP) project in the UK.

In the US, PDMPs are state-based database systems that collect information on controlled substance prescriptions in the US from 2002 [331, 332], and that information feedbacks to the healthcare providers to tackle doctor shopping and high-volume prescribing of controlled medicines. In addition to implementing systems that collect data on controlled substance prescriptions, the PDMPs covered education measures, engineering measures and enforcement measures in the 4E approach as PDMPs also provided the training about opioid overdose,

and 22 of the 49 states with PDMPs have legally mandated prescribers to query the system before prescribing opioids[315, 333].

However, due to the difference in the implementation process, regulatory and political environment, and available financial resources, there were substantial variations in the implementation and characteristics of PDMDs across the states[334, 335]. There were 57% of the states reported a more than one-week lag time from prescription filling to information appearing in the PDMP database, and only 65% of states shared data with at least one other states[334]. Despite the variations[334, 335], current evidence from SRs suggest that PDMPs are associated with the reduction in fatal overdose[336], but the effectiveness of PDMPs on opioid mortality varies between states[336-338].

To evaluate the association between the implementation of PDMPs and the change in fatal and nonfatal overdose, Fink *et al.* (2018) conducted a SR of observational studies that identified the before-and-after change in

nonfatal or fatal drug overdoses after a PDMP was implemented. From the 10 included studies, low-strength evidence (evaluated by limitations, directness, consistency, precision and reporting bias) suggested the implementation of PDMPs was associated with a reduction in fatal overdose. In the subgroup analysis, mandating prescribers to access their state's PDMPs system before prescribing controlled substance, the frequency of reporting and monitoring of non-scheduled medications, such as other analgesics were associated with the reduction in fatal overdose[336].

In Taiwan, in order to avoid potential opioid use disorders, prescribing opioids chronically to CNCP patients has been strictly regulated since 1996. According to the Taiwan Food and Drug Administration (TFDA), chronic opioid utilisation was defined as patients received opioids (including morphine, codeine, opium, pethidine, alfentanil, fentanyl, oxycodone, hydromorphone and buprenorphine) for more than 28 days in three months, or continuously been prescribed with opioid

prescriptions which lasted for more than 14 days. Chronic opioid utilisation requires advance approval, and chronic opioid users must be registered in the RACCDMU of TFDA. Furthermore, the controlled drug committee in the hospitals needed to evaluate the benefits and risks of chronic opioid therapy and report to TFDA every four months.

The policy about registering chronic opioid users in the RACCDMU of TFDA covered engineering measures and enforcement measures in the 4E approach. Due to the restrictive regulation, the annual numbers of new chronic opioid users between 2003 and 2012 were less than 100 patients and the overall number of chronic opioid users for CNCP reported to the TFDA's RACCDMU between 2003 and 2012 was 644[339]. Compared to the increasing prolonged opioid utilisation observed in western countries, underuse of opioids has been suggested in Taiwan[340-344]. However, similar to limited accessibility by regulation, once patients' pain was not well managed, physicians and patients would use alternative ways to bypass the measure[318], and this was exemplified the

fact that about half of chronic opioid users in 2008 and 2009 ever received opioids from emergency departments, and about 30% of clinical visits which an opioid has been prescribed happened in emergency departments[345].

In the UK, due to the increasing opioid prescribing and the variation in opioid prescribing across geographic region[146], the CROP project conducted a bimonthly enhanced audit, provided behavioural change techniques to physicians and submitted feedback reports on the number of opioid prescribing to practices in the ten Clinical Commissioning Groups of West Yorkshire [346].

Although the CROP project covered education measures and engineering measures in the 4E approach, this intervention was implemented at physician level rather than the individual patient[346]. Engineering measures are effective in removing the barriers of controlling increasing medication prescribing[347], but several barriers such as patient fear of relapse and withdrawal effects were related to

concerns from individual patients[348]. Although the effectiveness of the CROP project has not been evaluated, it is possible that it may have a limited effect on the deprescribing of opioids.

In our study, more than one quarter and 30% of opioid-related deaths had records of overdose and any substance abuse disorders from one year before opioid initiation to death. Also, more than a quarter of opioid-related fatalities did not receive any opioid in the final year before opioid-related death, which may indicate concerns related to opioid disposal or non-medical sources. That evidence indicated that opioid-related deaths in the UK involved problematic opioid users and there is an opportunity for early intervention to patients with high risk of opioid-related death.

Although this study found more than 70% of opioid-related deaths had records of medication review done by general practices in one year before opioid-related death occurred, the current information of

medication and individual's risks in the general practice system may be insufficient for physicians to identify the potential risk of misuse. Identifying history of problematic substance use before opioid initiation for opioid new users is recommended by prescribing guidance[5]. In the UK, the NDTMS dataset which is a registry organised by Public Health England includes adult patients who received treatment for problematic drug/alcohol use in England and their information about the history of substance use disorder and the treatment[349, 350]. However, this system cannot be linked with the general practice clinical system and hence there is no validated information source to inform physicians in primary cares about patients' history of substance abuse[351].

Although doctor shopping might not be an issue in the UK as primary care practices are the gatekeepers for delivering health care and most people generally register with one general practice near their home[352, 353], patients could receive opioids from secondary care, emergency departments and non-prescribing routes, such as over-the-counter. The

HES included details of hospital admission and emergency department attendances[354], but the HES database cannot be linked with general practices clinical system[355]. In addition, analgesics received from over-the-counter or other sources were not routinely recorded in the general practices clinical system[187].

Additional monitoring of non-scheduled drugs in PDMPs was associated with the reduction in fatal overdose[336]. Establishing a systematic and valid framework for using real-world evidence to inform clinical decision making is an emerging era in pharmacovigilance, and developing evidence-based guidance for managing the patients with high-risk of problematic opioid use is also crucial in the UK.

9.3.3. Clinical practice guidance and deprescribing of opioids

At local practice level, several suggestions, recommendations or policies (such as deprescribing) have been implemented in clinical practices to optimise opioid prescribing in both the US and the UK. Opioid prescribing guidance has been developed and applied to reduce opioid

prescribing from the 2000s[57-59]. Prescribing guidance is classified as an education measure within the 4E approach, but it only affects physicians' awareness and has limited effects on improving the quality of prescribing and clinical outcomes unless combined with other measures[315]. In fact, suboptimal compliance with the opioid prescribing guidance has been found in the US[356]. In the cross-sectional study conducted by Franklin *et al.* (2012), there was only a decrease in the number of opioid prescribing item after the launch of opioid prescribing guidance that highlighted an OMEQ dose 120 mg per day as a prescribing threshold, and the number of opioid overdose deaths still increased[60].

The reason of suboptimal compliance of opioid prescribing guidance might be because the guidance is based on observational studies with notable limitations, such as no adjustment of confounding factors and selected populations[19]. As opioid overdose deaths involving multiple determinants and complex mechanisms[45], the recommendations from prescribing guidance might be hard to apply in real practice as the

majority of opioid users were diagnosed with depression and anxiety and concurrently prescribed with CNS depressants.

Deprescribing was defined as the process of identifying and discontinuing medications in which existing or potential harms outweigh benefits [357, 358]. As long-term efficacy of persistent opioid utilisation is not supported by the evidence from published RCTs [93-99], and persistent opioid utilisation is also found to be associated with opioid-related deaths in this study, 'deprescribing of opioids' would be a potential choice to reduce opioid-related deaths for patients who are going to be persistent opioid users.

However, according to the results of a SR of RCTs identifying the efficacy of different methods (such as acupuncture) to achieve reduction or cessation of prescribed opioids for patients with CNCP, there was no evidence to support the efficacy of interventions to decrease opioid prescribing. It is worth to note that the sample size of all the included

RCTs is less than 100, and the majority of studies used subjective measures, such as self-reported questionnaire, rather than objective measures to quantify opioid use[300].

Besides, deprescribing of opioids may have unintended consequences on pain intensity or physical function. As pain management requires multiple-disciplinary interventions, to achieve successful opioid deprescribing, a comprehensive pain rehabilitation programs (CPRP) in the US which providing functional restoration and cognitive-behavioural treatment may help improve quality of life after opioid tapering. Although several observational studies have used real-world practices to evaluate the effectiveness of CPRP in the US, the majority of studies applied quasi-experimental study design to conduct before-and-after comparisons within study groups, and only patients who completed the rehabilitation program were included in the analysis[359-362]. Therefore, the effectiveness of CPRP in reducing opioid utilisation is still uncertain.

In the UK, the Improving the Wellbeing of People with Opioid Treated Chronic Pain (I-WOTCH) study is a RCT aiming to evaluate the effectiveness of a multicomponent self-management intervention in comparison to usual care on pain severity, daily activities, health-related quality of life and opioid use for strong opioids users with CNCP. The I-WOTCH study recruited patients from 100 general practices across North East London, North East and West Midlands England between September 2016 and September 2018 and will follow patients for one year. At the time of completing this thesis, this study is still on going, and hence the effectiveness of a multicomponent self-management intervention in deprescribing opioids was still unclear.

The attributes of successful deprescribing include changing prescriber behaviour, patient behaviour and its interaction, and a SR identifying the effect and feasibility of strategies of deprescribing from both RCTs and observational studies concluded that only intervention involved both physicians and patients were likely to be effective[363]. As there was no

theoretical framework which explained the linkage between intervention and behaviour change, Michie *et al*. (2011) proposed a behaviour system involving three essential conditions: capability, opportunity, and motivation (COM-B system) to explain the sources of behaviour. 'Capability' is defined as psychological and physical capacity such as knowledge and skills to engage the behaviour. 'Opportunity' considers all the factors that lie outside the individual that prompt the behaviour. 'Motivation' is defined as all the brain processes that energise and direct behaviour, which including emotional responding as well as analytical decision-making. By understanding capability, opportunity, and motivation and its interaction with behaviour, it will be more likely to change personal behaviour[364].

In order to deprescribe medication successfully, there were facilitators of deprescribing identified from the perspective of both patients and physicians, such as a lack of treatment effectiveness and clear methods and instructions to identify benefits and harms of therapy[348]. Several

barriers including fear of negative clinical consequence and lack of confidence on patients' conditions have been also identified[348].

Physicians deprescribe opioids based on benefits and risks of opioid treatment, and being able to identify benefits and harms of therapy has been suggested as a facilitator of deprescribing[5, 19, 348]. However, studies have suggested that physicians have concerns on chronic opioid treatment due to the fear of abuse and difficulty to determine the effect of chronic opioid treatment on pain relief as pain is an objective symptom[365, 366]. To provide chronic pain patients with a timely and skilled service to reduce the causes of pain and to enable them to manage their pain, specialised services for pain management have been implemented in primary care in England [367]. However, there is no system or registry that has longitudinally followed pain condition, functional improvement and quality of life after opioid initiation.

Regarding the risk of serious adverse events of opioid therapy, a registry

for patients who ever received opioid daily dose more than OMEQ 120 mg/day has been suggested[146], but the result from this study showed that opioid daily dose more than OMEQ 120 mg/day was not associated with greater opioid-related deaths in the UK. As persistent opioid utilisation was related to an increased risk of opioid-related death in this study, a registry for patients who ever received opioids persistently might be needed.

9.4. Recommendations to facilitate opioid deprescribing in practice

There were suggestions to facilitate opioid deprescribing by specialised services for pain management. According to COM-B system, a patient-managed longitudinal system which recording pain intensity and analgesics received from over-the-counter or other sources is an 'opportunity' for physicians as it could increase physicians' 'capability' to deprescribe opioids[364]. As a lack of long-term effectiveness of persistent opioid utilisation has been found in RCTs, a patient-managed system

would also facilitate patients to deprescribe opioids due to the lack of treatment effects[348].

A system recording information for predicting the risk of opioid-related harm and informing the management of conditions is needed to facilitate opioid deprescribing. Based on 4E approach, a linkage of prescribing records of opioids from secondary cares and emergency departments with general practice clinical systems is an engineering measure which may be effective on removing barriers of deprescribing opioids such as lacking confidence on patients' conditions[347, 348]. Information about the history of problematic substance use should also be available in the general practice clinical systems to indicate patients with higher risk of opioid-related deaths.

9.5. Early prevention of opioid-related deaths and evaluation of control substance classification

This study showed that about half of opioid-related deaths ever received medication reviews, but more than a quarter of opioid-related fatalities did not receive any opioid in the final year before opioid-related death. Those results indicate concerns related to opioid disposal, and it seems medication review had only a limited effect on controlling opioid diversion and opioid-related deaths. Diversion was defined as 'the transfer of a controlled substance from a lawful to an unlawful channel of distribution or use', and implies potential concerns about opioid abuse as one of the criteria to define abuser is opioid use without a prescription[280]. To achieve early prevention of opioid-related deaths, control possible opioid abuse and facilitate opioid deprescribing, further research needs to explore attitudes and knowledge about opioid disposal and the use of prescribing opioids from the perspective of potential prescribing opioid abusers. Opioid utilisation needs to be investigated for patients with high risk of opioid-related deaths such as

patients with substance abuse or overdose history.

This study evaluated the short-term impacts of tramadol classification, and the long-term influence of tramadol classification on drug-misuse deaths and utilisation of other opioids or medications with abuse potential remain unknown. In fact, although the number of tramadol-related deaths decreased from 2015 and remain stable until 2017, the number of opioid-related deaths involving codeine and fentanyl keep increasing from 2015[368]. In addition to opioids, the number of drug-misuse deaths involving substance with abuse potentials, such as BZDs, antipsychotics, Z-drugs, SSRIs, pregabalin and gabapentin also increased between 2010 to 2017 in the England and Wales[368]. As pregabalin and gabapentin were recommended to be classified as Class C Control Substances[330], further studies should apply IPD to evaluate the effects on the utilisation of pregabalin, gabapentin and other sedatives and its consequence on the change in drug-related deaths.

9.6. Conclusion

In conclusion, tramadol classification has impacts on the increasing tramadol prescribing and tramadol-related deaths. However, the effects of tramadol classification seem predominantly associated with the changing prevalence and incidence of tramadol users, and hence it is still unclear whether limiting accessibility of opioids would increase the utilisation of medications with abuse potential and that are also indicated for pain relief.

Increasing tramadol prescribing was related to the increase in the number of tramadol-related deaths in England and Wales in the past decade. As the majority of opioid-related deaths in the UK received opioids with low dose but long duration, opioid-related deaths were associated with persistent opioid utilisation rather than opioid daily dose more than OMEQ 120 mg/day. However, there is no system or registry longitudinally following pain diagnoses and analgesics received from over-the-counter or other sources, and the prescribing records in

secondary care and the official registry of problematic substance users cannot be linked with general practice clinical systems. To facilitate opioid deprescribing in specialised services, an information system helping to identify benefits and risks of opioid treatment and evaluation of specialised services on opioid deprescribing and opioid-related deaths are needed.

In addition to the utilisation of prescribing opioids, most opioid-related fatalities were diagnosed with substance abuse disorder and psychological illnesses, had a history of overdose and received CNS sedatives concurrently with opioids. In addition, more than a quarter of opioid-related fatalities did not receive any opioid in the final year, which implied an issue related to opioid diversion. Further research needs to explore opioid utilisation and attitude about opioid disposal, diversion and concurrent sedatives from potential prescribing opioid abusers.

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Appendix

Appendix 1. ISAC approval from CPRD

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

<table>
<tr><td colspan="4">CONFIDENTIAL by e-mail</td></tr>
<tr><td>PROTOCOL NO:</td><td colspan="3">12_007RA</td></tr>
<tr><td>PROTOCOL TITLE:</td><td colspan="3">Trends and patterns of opioid utilisation in a UK primary care population</td></tr>
<tr><td>APPLICANT:</td><td colspan="3">Li-Chia Chen, BPharm, MSc, PhD.
Assistant Professor in Medicine Use, University of Nottingham
Email: li-chia.chen@nottingham.ac.uk</td></tr>
<tr><td>APPROVED
☒</td><td>APPROVED WITH COMMENTS (resubmission not required)
☐</td><td>REVISION/ RESUBMISSION REQUESTED
☐</td><td>REJECTED
☐</td></tr>
<tr><td colspan="4">INSTRUCTIONS:
Please include your response/s to the Reviewer's feedback below <u>only</u> if you are required to Revise/ Resubmit your protocol.
Protocols with an outcome of 'Approved' or 'Approved with comments' <u>do not</u> require resubmission to the ISAC.

REVIEWER COMMENTS:
Protocol 12_007RA is approved.</td></tr>
<tr><td colspan="2">DATE OF ISAC FEEDBACK:</td><td colspan="2">12/08/2016</td></tr>
<tr><td colspan="2">DATE OF APPLICANT FEEDBACK:</td><td colspan="2"></td></tr>
</table>

For protocols approved from 01 April 2014 onwards, applicants are

required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.

** Please refer to the ISAC advice about protocol amendments provided below**

Appendix 2. Segmented regression model

$Y_t = \beta_0 + \beta_1 * time + \beta_2 * tramadol\ classification + \beta_3 * time\ after\ tramadol\ classification$

$\boldsymbol{Y_t}$ is monthly tramadol utilisation, measured as monthly DDD between October 2010 and September 2015 from NHS digital practice-level dispensing data and CPRD (further stratified by incident and prevalent users).

time refers to time from October 2010 to September 2015 in a monthly base.

Tramadol classification is a binary variable and 1 to denote the time from June 2014.

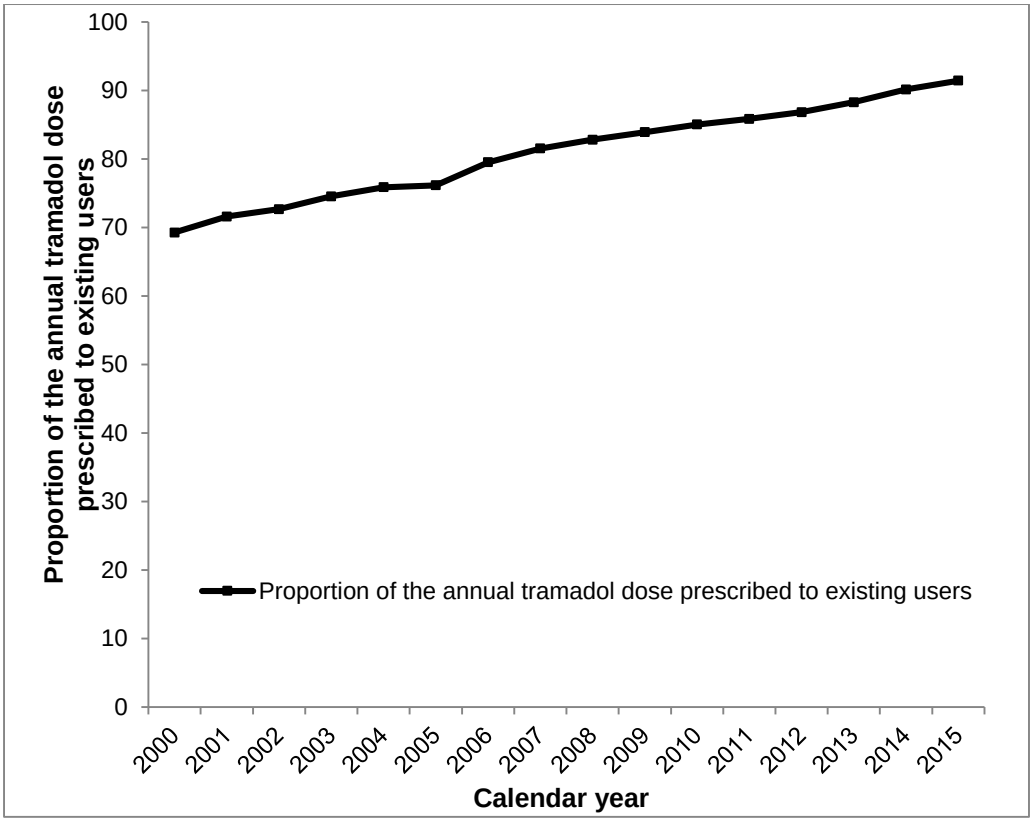
Time after tramadol classification refers to time from June 2014 to September 2015 in a monthly base.

The baseline trend of monthly tramadol utilisation before classification (β1), the change in the levels of monthly utilisation (β2) and the change in trend of monthly tramadol utilisation after classification (β3) were tested.

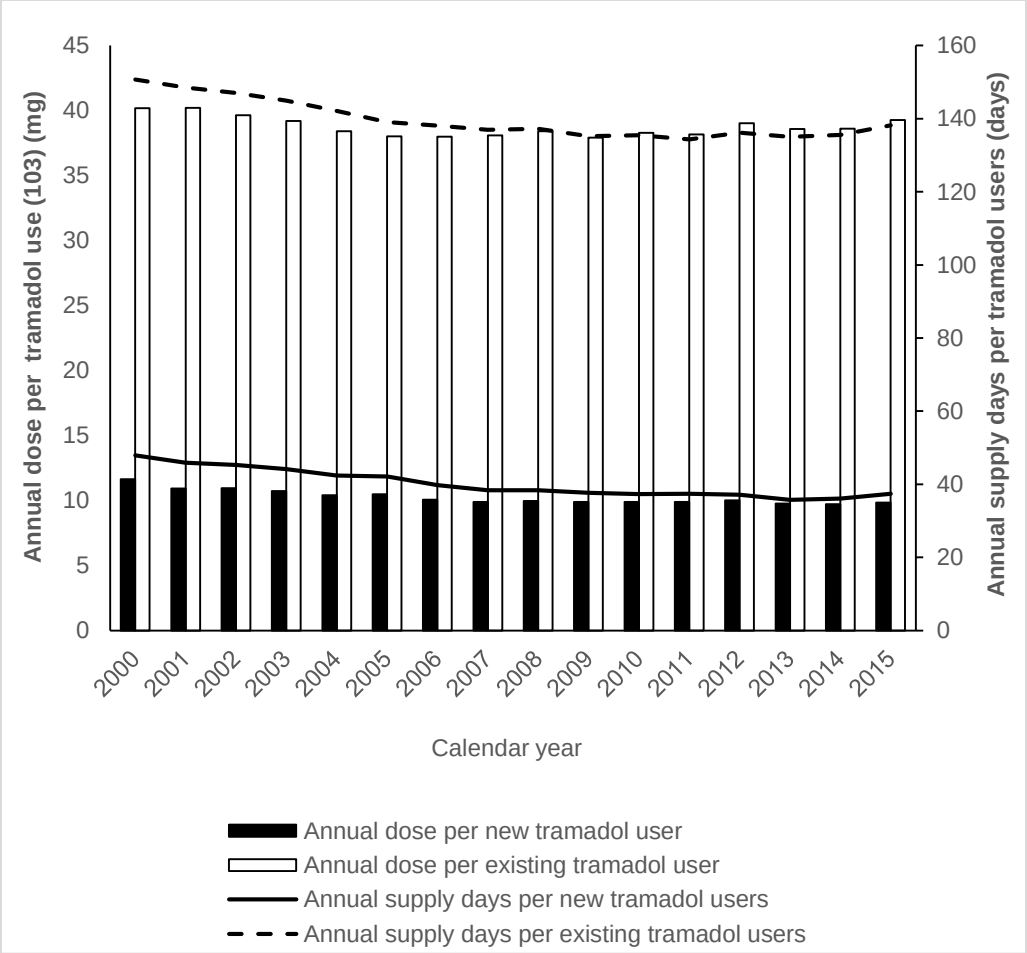
Additional time points in the policy development, including the publication of ACMD recommendation (February 2013), commencing

public consultation about tramadol classification (July 2013) and publishing results of the public consultation (March 2014) were included in the segmented regression model for sensitivity analysis.

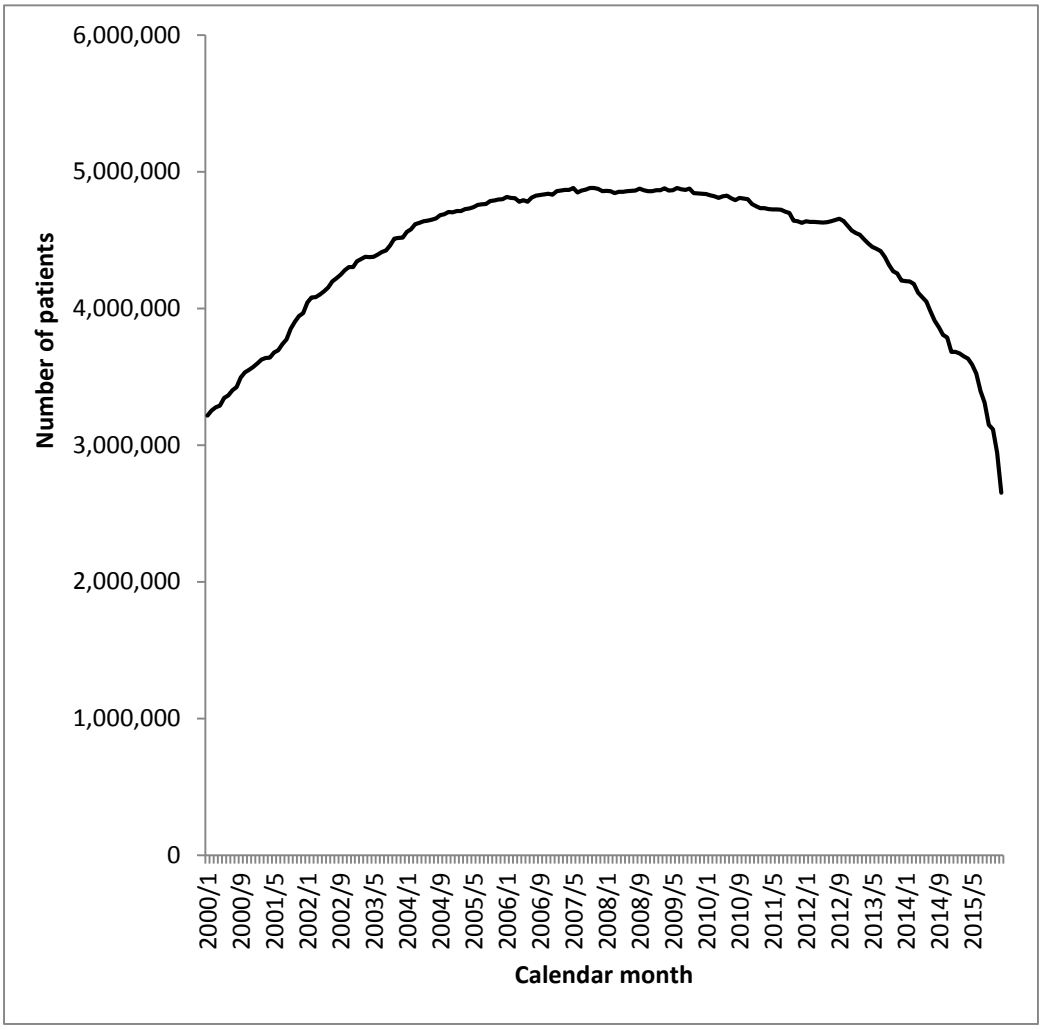
Appendix 3. Proportion of the annual tramadol dose prescribed to existing users



Appendix 4. Annual dose and supply days between existing and new tramadol users



Appendix 5. Monthly number of active patients registered in the CPRD



Appendix 6. The International Classification of Diseases-the tenth version (ICD-10) diagnosis codes to define drug-related deaths and narcotics involved in drug-related deaths

Drug-related death	
ICD-10	Description
F11–F16, F18–F19	Mental and behavioural disorders due to drug use (excluding alcohol and tobacco)
X40–X44	Accidental poisoning by drugs, medicaments and biological substances
X60–X64	Intentional self-poisoning by drugs, medicaments and biological substances
X85	Assault by drugs, medicaments and biological substances
Y10–Y14	Poisoning by drugs, medicaments and biological substances, undetermined intent
Poisoning by narcotics	
ICD-10	Description
T40.0	Poisoning by narcotics and psychodysleptics-Opium
T40.1	Poisoning by and adverse effect of heroin
T40.2	Poisoning by narcotics and psychodysleptics- Other opioids
T40.3	Poisoning by narcotics and psychodysleptics- Methadone
T40.4	Poisoning by narcotics and psychodysleptics- Other synthetic narcotics
T40.6	Poisoning by narcotics and psychodysleptics- Other and unspecified narcotics

Appendix 7. The International Classification of Diseases-the tenth version (ICD-10) diagnosis codes to define tramadol-related adverse events

Hypoglycaemia	
ICD-10	Description
E15	Nondiabetic hypoglycaemic coma
E16.0	Drug-induced hypoglycaemia without coma
E16.1	Other hypoglycaemia
E16.2	Hypoglycaemia, unspecified
Hyponatremia	
ICD-10	Description
E87.1	Hypo-osmolality and hyponatraemia
E22.2	Syndrome of inappropriate secretion of antidiuretic hormone
Seizure	
ICD-10	Description
G40.X	Epilepsy
G41.X	Status epilepticus

Appendix 8. The International Classification of Diseases-the tenth version (ICD-10) diagnosis codes to define serotonin syndrome

Hypoglycaemia	
ICD-10	Description
E15	Nondiabetic hypoglycaemic coma
E16.0	Drug-induced hypoglycaemia without coma
E16.1	Other hypoglycaemia
E16.2	Hypoglycaemia, unspecified
Hyponatremia	
ICD-10	Description
E87.1	Hypo-osmolality and hyponatraemia
E22.2	Syndrome of inappropriate secretion of antidiuretic hormone
Seizure	
ICD-10	Description
Clonus	
ICD-10	Description
R25	Abnormal involuntary movements
R25.8	Other and unspecified abnormal involuntary movements
G25.3	Myoclonus
Hypertonia	
ICD-10	Description
M62.8	Other specified disorders of muscle
M62.9	Disorder of muscle, unspecified
M62	Other disorders of muscle
R29.8	Other symptoms and signs involving the nervous and musculoskeletal systems
R29	Other symptoms and signs involving the nervous and musculoskeletal systems
Ocular clonus	
ICD-10	Description
H51.8	Other specified disorders of binocular movement
H51.9	Disorder of binocular movement, unspecified

H51	Other disorders of binocular movement
H55	Nystagmus and other irregular eye movements
H57.0	Anomalies of pupillary function
H57	Other disorders of eye and adnexa
Agitation	
ICD-10	Description
R45.1	Restlessness and agitation
F43.0	Acute stress reaction
Diaphoresis	
ICD-10	Description
R61	Hyperhidrosis
R61.0	Localized hyperhidrosis
R61.1	Generalized hyperhidrosis
R61.9	Hyperhidrosis, unspecified
Hyperreflexia	
ICD-10	Description
R29.2	Abnormal reflex
Fever	
ICD-10	Description
R50	Fever of other and unknown origin
R50.2	Drug-induced fever
R50.8	Other specified fever
R50.9	Fever, unspecified

Appendix 9. Characteristics applied to disease risk score calculation

Variable	Definition
Demographic Characteristics	
Age	Patients' age when opioid-related deaths occurred
Gender	Patients' gender recorded in the patient file of CPRD
Townsend score	Socioeconomic status identified from the linkage data which included Townsend score calculated at LSOA level using unadjusted 2001 census data
Chronic pain	
Low back pain	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Arthritis	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Neuropathic pain	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Fibromyalgia	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Other pain conditions	
Surgical pain	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Abdominal pain	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred

Headache	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Pancreatitis	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Migraine	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Kidney stone	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Post-operative pain	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Psychological illnesses	
Depression	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Sleep disorder	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Anxiety	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Panic	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Cardiovascular diseases	
Any cardiovascular	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths

disease	occurred
Hypertension	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Diabetes	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Respiratory disease	
Asthma	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Upper Respiratory Infection	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Shortness of breath	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Substance abuse disorder	
Alcohol abuse disorder	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Other substance abuse disorder	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Other	
Medication review	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths occurred
Overdose	Identified by medication codes from the CPRD clinical data in one year before opioid-related deaths

	occurred
Cancer	Any record identified by medication codes from the CPRD clinical data before opioid-related deaths occurred

Appendix 10. Model explored association between opioid-related deaths and persistent opioid utilisation in any of the three patient-years

Medicine utilisation	Category	aOR (95%CI)	p-value
Persistent opioid utilisation in any of the three patient-years	No	1 (reference)	0.0042
	Yes	1.9 (1.2, 2.9)	
BZD	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	3.6 (2.1, 6.1)	
	>1 DDD	6.4 (4.0, 10.3)	
Gabapentin/ pregabalin	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	1.6 (0.91, 2.9)	
	>1 DDD	5.9 (2.7, 12.9)	
Tricyclic antidepressants	0 DDD	1 (reference)	0.0332
	0< to ≤0.5 DDD	1.1 (0.63, 1.9)	
	>0.5 DDD	2.0 (1.2, 3.5)	
Antipsychotics	No	1 (reference)	<0.0001
	Yes	4.3 (2.5, 7.2)	

(Note) BZD: benzodiazepine

Appendix 11. Model explored association between opioid-related deaths and persistent opioid utilisation in all of the three patient-year

Medicine utilisation	Category	aOR (95%CI)	p-value
Persistent opioid utilisation in all of the three patient-years	No	1 (reference)	0.078
	Yes	1.7 (0.94, 3.1)	
BZD	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	3.6 (2.1, 6.1)	
	>1 DDD	6.5 (4.0, 10.5)	
Gabapentin/ pregabalin	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	1.6 (0.91, 3.0)	
	>1 DDD	6.0 (2.7, 13.2)	
Tricyclic antidepressants	0 DDD	1 (reference)	0.0296
	0< to ≤0.5 DDD	1.1 (0.63, 1.9)	
	>0.5 DDD	2.1 (1.2, 3.6)	
Antipsychotics	No	1 (reference)	<0.0001
	Yes	4.3 (2.5, 7.3)	

(Note) BZD: benzodiazepine

Appendix 12. Model explored association between opioid-related deaths and persistent opioid utilisation in the second or third but not in the first patient-year

Medicine utilisation	Category	aOR (95%CI)	p-value
Persistent opioid utilisation in the second or third but not in the first patient-year	No	1 (reference)	0.048
	Yes	1.7 (1.0, 2.9)	
BZD	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	3.6 (2.1, 6.2)	
	>1 DDD	6.4 (3.9, 10.3)	
Gabapentin/ pregabalin	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	1.6 (0.90, 2.9)	
	>1 DDD	5.9 (2.7, 12.9)	
Tricyclic antidepressants	0 DDD	1 (reference)	0.0373
	0< to ≤0.5 DDD	1.1 (0.63, 1.9)	
	>0.5 DDD	2.0 (1.2, 3.5)	
Antipsychotics	No	1 (reference)	<0.0001
	Yes	4.2 (2.5, 7.2)	

(Note) BZD: benzodiazepine

Appendix 13. Model explored association between opioid-related deaths and persistent opioid utilisation in the final patient-year

Medicine utilisation	Category	aOR (95%CI)	p-value
Persistent opioid utilisation in the final patient-year	No	1 (reference)	0.003
	Yes	3.3 (1.5, 7.4)	
Benzodiazepine	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	3.6 (2.1, 6.2)	
	>1 DDD	6.7 (4.1, 10.8)	
Gabapentin/ pregabalin	0 DDD	1 (reference)	<0.0001
	0< to ≤1 DDD	1.6 (0.91, 2.9)	
	>1 DDD	6.4 (2.9, 14.1)	
Tricyclic antidepressants	0 DDD	1 (reference)	0.0244
	0< to ≤0.5 DDD	1.1 (0.64, 1.9)	
	>0.5 DDD	2.1 (1.2, 3.6)	
Antipsychotics	No	1 (reference)	<0.0001
	Yes	4.3 (2.5, 7.3)	

(Note) BZD: benzodiazepine

Appendix 14. The product codes of tramadol preparations in the CPRD

Please refer to attached file: 180908_APP14_tra product code_TCC.xlsx

Appendix 15. The product codes of opioid preparations in the CPRD

Please refer to attached file: 180908_APP15_op product code_TCC.xlsx

Appendix 16. The medication codes of comorbidities in the CPRD

Please refer to attached file: 180908_APP16_comorbidity medication code_TCC.xlsx

Appendix 17. The product codes of sedatives preparations in the CPRD

Please refer to attached file: 180908_APP17_sedatives product code_TCC.xlsx

Appendix 18. The product codes of serotonergic agents in the CPRD

Please refer to attached file: 180908_APP18_serotonergic agent product code_TCC.xlsx