Swansea University
Prifysgol Abertawe
2021

Trends in Opioid Prescribing for Non-Cancer Pain and Associated Resource Utilisation in Wales

Submitted to Swansea University in fulfilment of the requirements for the Degree of Doctor of Philosophy

Emma Davies
BSc MPharm

Yn olaf, mae’n cael ei wneud

Summary

Background

Opioid prescribing in the UK has increased significantly since the start of the millennium and has been associated with a rise in chronic pain reporting. In Wales, despite concern about rising rates of opioid analgesic prescribing, no detailed examination of the data had been undertaken to assess the changes in prescribing and its consequent impact on the population.

Methods

In this study, anonymised, individual level data of people diagnosed with non-cancer pain in Wales was extracted from the Secure Anonymised Information Linkage (SAIL) Databank and used to scrutinise opioid analgesic prescribing trends in people aged 18 years and over, establish whether legislation or clinical guidance impacted on those trends and examine associations with increased healthcare use. The study was conducted in two phases. Phase 1 included a retrospective, repeated cross-sectional analysis of opioid analgesics issued from Primary Care, stratified by gender, age and socioeconomic status. Phase 2 of the study evaluated differences in healthcare service use and costs between individuals receiving opioids for defined non-cancer pain-related diagnoses and matched patients not receiving opioids.

Results

Total opioid prescribing increased by 43.6% and strong opioids by 306.2% between 2005 and 2015. Women received 1.5 times more prescriptions than men. Increasing age was associated with higher prescribing rates. People in the most deprived areas received 2.4 times more prescriptions than in least deprived. People receiving opioid prescriptions accessed primary care four times more frequently than controls and had twice the number of hospital admissions. Opioid prescription was associated with 41% higher healthcare costs than noted in controls.

Conclusion

This research highlights the need to develop a national strategy to address pain management and opioid stewardship in Wales. We must consider how to address the wide variability observed, particularly between areas of differing socioeconomic status. Further research should investigate what underlies continued opioid prescribing and how alternative strategies can be implemented in practice to reduce population harm and optimise the use of limited healthcare resources.

Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed  ……(candidate)

Date …24 September 2021……..

Statement 1

This thesis is the result of my own work, except where otherwise stated. The work for this thesis was carried out at the College of Health and Human Sciences, Swansea University, Wales with data extracted from the Secure Anonymised Information Linkage (SAIL) Databank, College of Medicine, Swansea University. Other sources are acknowledged giving explicit references. A bibliography is appended.

Signed …  ……(candidate)

Date ……24 September 2021……..

Statement 2

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed …  ……(candidate)

Date ……24 September 2021……..

Table of contents

Acknowledgements

I would like to thank above all, my supervising team, Professors Ceri Phillips and Jaynie Rance who supported and guided this research and encouraged me to continue through some difficult times. Drs Berni Sewell and Mari Jones, who took me on and have been incredibly patient, helped shape my thinking and made me believe I could be a researcher after all.

In the College of Health and Human Sciences, Maria Davis and Katie Retallick for their tireless support of all of us post-grads. Maddie, Sara, Caitlin, Carol, Alyson and Amy for their friendship, laughter and coffee.

Thanks also to my 'housekeeper', Dr Cathy Price, who is always there when I need her and was again. Dr Karen Hodson, who has guided me throughout my career and continues to do so. Professor Ann Taylor and Dr Sue Jeffs for reminding me to pull myself together and get on with it! Similarly, Dr Roger Knaggs, who has quietly cleared the path for me and many others to follow.

I gratefully acknowledge the funding from Pharmacy Research UK. This report is independent research, commissioned by Pharmacy Research UK. The views expressed in this publication are those the author and not necessarily those of Pharmacy Research UK. I would particularly like to thank Desh Mofidi for providing me with support and advice, well beyond his job description.

Thank you, Research Capacity Building Collaboration Wales (RCBC), for providing financial support for my PhD fellowship and personal support through the Community of Scholars. Special mention to Nic, Liba, Helen, Nicole, Jess and Ed.

This study makes use of anonymized data generated by the Secure Anonymized Information Linkage (SAIL) system, which is part of the national e-health records research infrastructure for Wales. I would like to acknowledge all the data providers who make anonymised data available for research and also the staff who undertook the data extraction on my behalf.

Finally, Chris, Gethin and Awen xxx

List of Tables

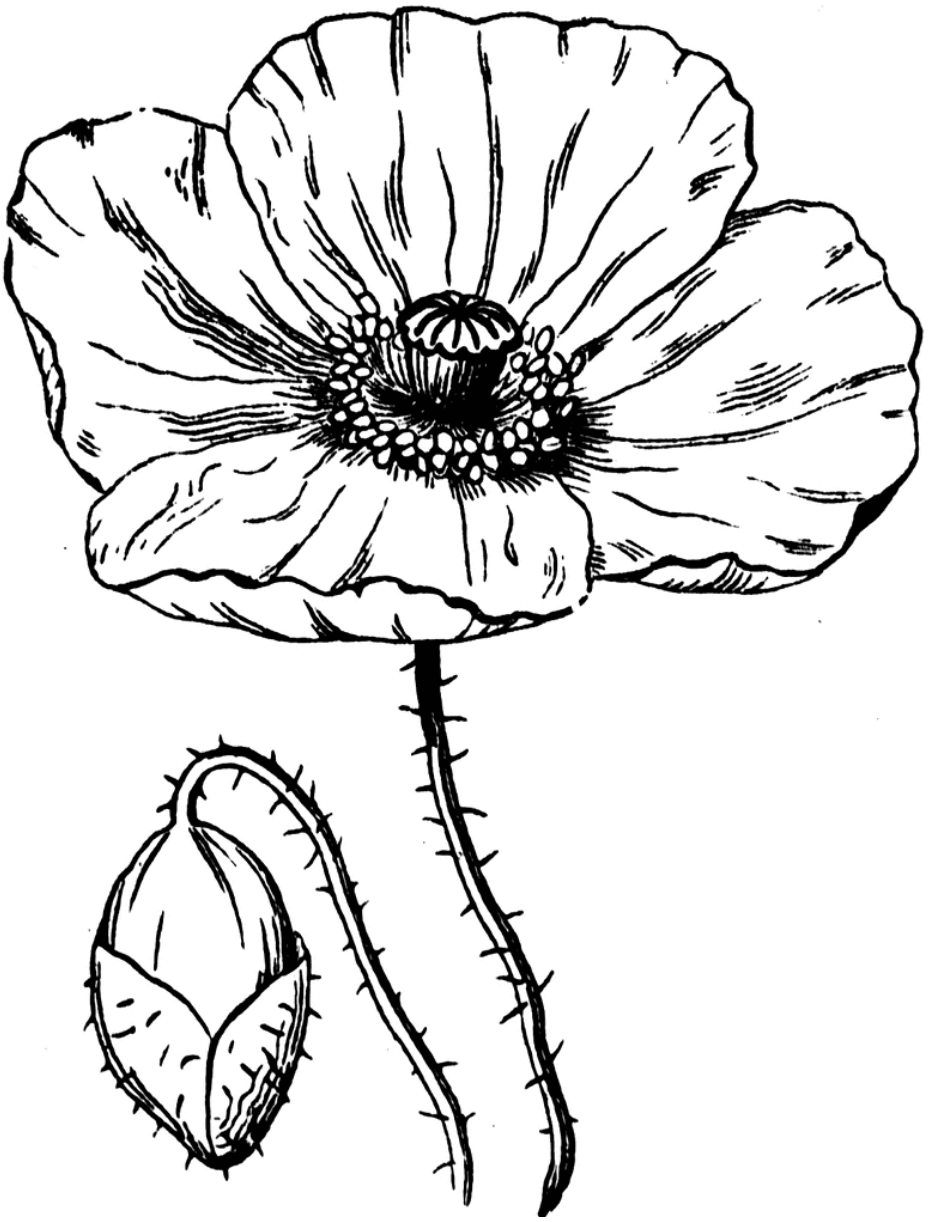
List of Figures

List of abbreviations

95% CI	95% Confidence Interval
ABMUHB	Abertawe Bro Morgannwg University Health Board
ABUHB	Aneurin Bevan University Health Board
ADDE	Annual District Death Extract
ADE	Adverse Drug Event
AICc	corrected Akaike Information Correction
ALF	Anonymised Linkage Field
ALF-E	Anonymised Linkage Field with additional encryption
ANOVA	Analysis of Variance statistical test
BCUHB	Betsi Cadwaladr University Health Board
BNF	British National Formulary
CASPA	Comparative Analysis System for Prescribing Audit
CCI	Charlson Comorbidity Index
CHC	Community of Health Councils for Wales
CIPHER	Centre for Improvement in Population Health through e-Records Research
CMM	Centred moving mean
CNCP	Chronic non-cancer pain
CNMP	Chronic non-malignant pain
CP	Chronic pain
CPRD	Clinical Practice Research Datalink
CTUHB	Cwm Taf University Health Board
CVUHB	Cardiff and Vale University Health Board
DALYs	Disability Adjusted Life Years
DDD	Defined Daily Dose
DHCW	Digital Health and Care Wales
DUP	Drug usage period
EU	European Union
FPM	Faculty of Pain Management
GBD	Global Burden of Disease study

GBTM	Group based trajectory model
GP	General Practitioner
GPPC	General Practice Primary Care
HB	Health Board
HDUHB	Hywel Dda University Health Board
HES	Hospital Episode Statistics
HR	Hazard ratio
HRG 3.5	Healthcare Resource Groups version 3.5 (NHS England)
HRG 4	Healthcare Resource Groups version 4 (NHS England)
HSE	Health Survey for England
ICD-10	International Statistical Classification of Diseases and Health-related problems, 10th revision
IGRP	Information Governance Review Panel (SAIL)
ISE	Individual seasonal effect
LSOA	Lower Super Output Area
MESH	Medical Subject Headings
MLE	Maximum likelihood method (for time series analysis)
mg	milligrams
MM	Moving mean
NICE	National Institute for Health and Care Excellence
NPI	National Prescribing Indicator
NPIs	National Prescribing Indicators
OLS	Ordinary Least Squares
OMEQ	Oral morphine equivalent dose
$OMEQ_e$	Estimated oral morphine equivalent dose
ONS	Office for National Statistics
OPCS-4	OPCS Classification of Interventions and Procedures version 4
OR	Odds Ratio
PHIH	Prudent Healthcare Intelligence Hub
PP	Prescription period
PRUK	Pharmacy Research UK
PTHB	Powys Teaching Health Board

QALY	Quality-adjusted Life Year
RALF	Residential Anonymised Linking Field
RMSE	Root mean squared error
SAIL	Secure Anonymised Information Linkage databank
SIGN	Scottish Intercollegiate Guideline Network
SPSS	Statistical Package for Social Sciences (historical name, now commonly just referred to as SPSS)
SQL	Structured Query Language
TSA	Time Series Analysis
TOPAS	Trends in Opioid Prescribing and Associated Resource Utilisation in Wales
UK	United Kingdom
USA	United States
WDSD	Welsh Demographic Service Dataset
WG	Welsh Government
WHO	World Health Organisation
WLGP	Welsh Longitudinal General Practice
WMID	Welsh Index of Multiple Deprivation
YLD	Years Lived with Disability



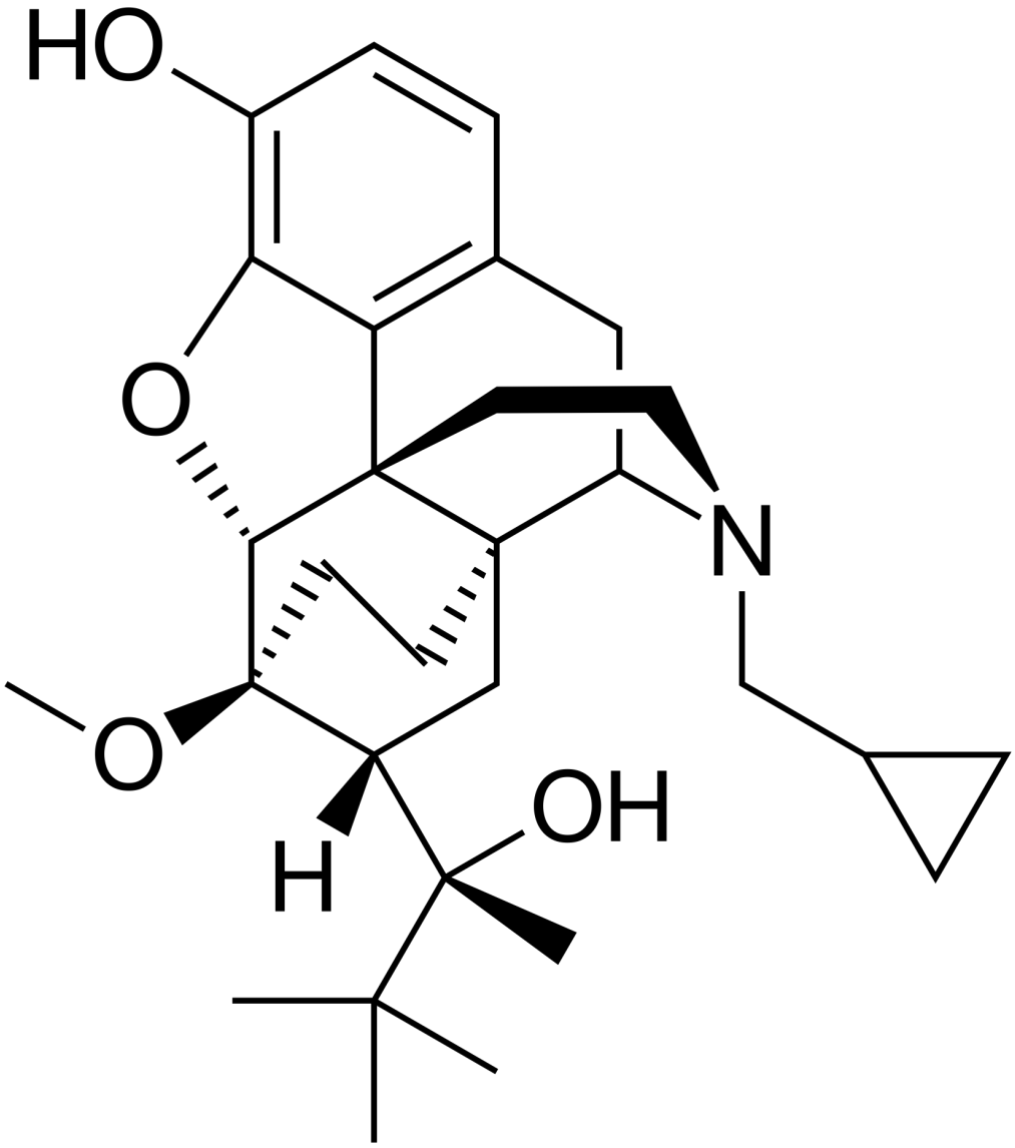
"When pain was unavoidable, we tolerated it. When pain became avoidable, it became intolerable. What we have created, with all of our painkillers and pain management strategies, is an intolerance and increased sensitivity to pain."
Joanne Dahl, speaking in Southampton, 2007

Personal Statement

I have worked as a pain management specialist pharmacist since early 2006, working initially under the generous supervision of Dr Cathy Price in Southampton. Shortly after I started working in pain management, concerns from North America about the misuse of prescribed opioid analgesics began to gather pace. This set about a change in chronic pain management around the world. Mindful practitioners began to reassess their own practice and realise that whilst opioids, and analgesics in general, may be helpful for some people, it was perhaps a smaller percentage than had first been thought. Chronic pain management is a long-term pursuit. Enduring harms associated with opioids, including immune dysfunction, endocrine dysfunction, depression, and anxiety all began to feel a little more real. The question of whether opioids do more harm than good has become a topic of conversation at most chronic pain meetings and conferences.

It appears there is consensus in the UK that opioids are unlikely to benefit most people living with persistent pain in the long-term. We must be wary, however, not to remove them from those who do gain advantage. Increasingly, I spend my time in practise supporting people to manage long-term health conditions that opioids have contributed to. People who have been convinced that opioids are their only option, despite little evidence their lives have improved since taking them. Despite these concerns, little information exists about the potential numbers of people developing health problems other than misuse, from prescribed opioids in the United Kingdom. There is nothing at all available from Wales on this issue. Consequently, I had to start at the beginning and establish some baseline data on trends in opioid prescribing in Wales. I then, looked at drug selection and duration of prescribing, as this may help develop better targeted prescribing interventions nationally. Finally, I wanted to examine whether opioid use was associated with greater healthcare use in Wales and how much that was likely to be costing the National Health Service. Having an indication of the likely costs may assist in rethinking how limited funds are best used, supporting the large numbers of people we know live with pain in Wales.

Chapter 1
Introduction



"You can't go back and change the beginning, but you can start where you are and change the ending."
C S Lewis

Chapter 1 - Introduction

1.1 Chapter overview

This chapter provides a narrative of published literature relating to pain and the use of opioid analgesics. A pragmatic review of the literature was conducted using medical subject headings (MESH) to systematically search literature databases (Figure 1.1). Quality was appraised using Critical Appraisal Skills Programme (CASP) checklists. Snowballing was also used, especially in regard of determining seminal references, and grey literature was searched using Googlescholar and directly on Government and other organisations websites.

Included in this chapter is a discussion of pain, how it is defined and why it is important in societal and economic terms. Then, the management of pain and the place of opioid analgesics in it. In particular, the current acceptability of opioid use for chronic pain is considered, alongside concerns about potential adverse effects and long-term harms. Factors which are considered to impact on the prevalence of pain and consequently, possibly linked to opioid prescribing will also be covered. These include gender, age, socioeconomic deprivation, legislation and clinical guidance. Finally, the chapter ends with an explanation of why the research presented in the thesis was needed and how the research questions were generated. This introduction is intended to set the scene for the rest of the study and will be referred back to as the thesis progresses.

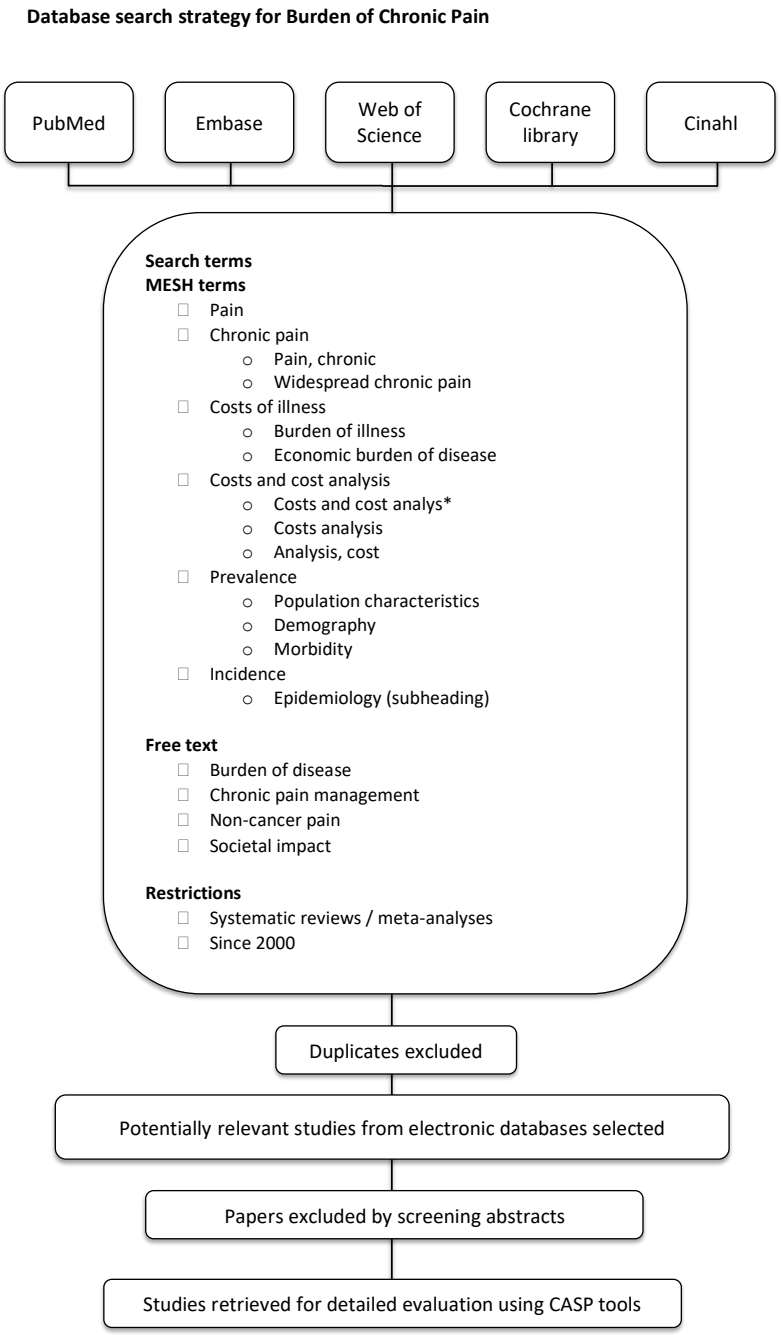


Figure 1.1: Example literature database search strategy using MESH headings

1.2 Defining pain

Pain is defined by the International Association for the Study of Pain (IASP) as, '*an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage'* (Nicholas et al. 2019).

Acknowledging an emotional component to the episode of pain leads to it being subjective and individual to the person having the experience (Eccleston 2011). Consequently, understanding, treating and managing pain from any source becomes reliant on self-report and this places it apart from many other conditions in medicine and undoubtedly is one reason it can be difficult to manage in clinical practice (Raffaeli and Arnaudo 2017).

Pain can be sub-divided into acute, malignant and chronic-non-malignant, which may then be further described by virtue of a known or postulated underlying source (Treede et al. 2015; Nicholas et al. 2019; Smith et al. 2019). Simply put, acute pain is of short duration and commonly caused by trauma of some sort (e.g., standing on a drawing pin, following a sports injury, broken bones or after surgery). The duration of pain expected from acute incidents are generally acknowledged to be related to the time needed to heal (Carr and Goudas 1999; Johnson et al. 2013). Malignant pain arises from cancer and is often referred to as chronic malignant pain, as its duration is generally linked to the period of disease, which is of a long-term nature (Cooney et al. 2013; Lozano-Ondoua et al. 2013; Bennett et al. 2019). Lastly, chronic non-malignant pain (CNMP) describes pain experienced for longer than three months, or beyond the time that healing would have been expected (Nicholas et al. 2019). Chronic non-malignant pain may develop following an episode of acute pain, could be a symptom of an underlying condition such as osteoarthritis or diabetes, but may also be thought of as a condition in its own right (Department of Health 2012) given it often persists after an original insult has resolved or may even occur for seemingly no known reason.

1.3 Defining chronic pain

Whilst acute pain is experienced by the majority of people at some point in life, pain that persists is a source of suffering estimated to affect up to 20% of people worldwide (IASP 2019). Chronic pain is an overarching term, which clinically, can encompass a range of presentations of pain and other symptoms. The International Association for the Study of Pain (IASP) agreed diagnostic criteria

for a range of chronic pain conditions to be included in the International Classification of Diseases version 11 (ICD-11) and which will come into practice in 2022 (Nugraha et al. 2019a). Chronic primary pain, is newly designated a disease. It is characterised by pain persisting for more than 3 months which, cannot be attributed to another condition (Nicholas et al. 2019). Other symptoms emotional distress and / or functional disability (Nicholas et al. 2019) which has been described by the National Institute of Health and Care Excellence (NICE) as being disproportionate to any underlying pathology, (National Institute for Health and Care Excellence 2021). Conditions included under the diagnostic banner of chronic primary pain include fibromyalgia and complex regional pain syndrome (Nicholas et al. 2019; National Institute for Health and Care Excellence 2021).

Chronic primary pain can co-exist with other chronic pain conditions and IASP have classified six secondary chronic pain conditions. Other new additions to ICD-11 include chronic cancer-related pain, caused by cancer or its treatment (Bennett et al. 2019) and chronic post-surgical or post-traumatic pain, which may result from or worsen as a consequence of tissue trauma (Schug et al. 2019). Chronic secondary musculoskeletal pain in bones, joints and tendons (Perrot et al. 2019), visceral pain which originates from internal organs (Aziz et al. 2019) and headache or orofacial pain (Benoliel et al. 2019) are not new classifications but have had characteristics updated for ICD-11. Chronic neuropathic pain has been in previous ICDs, but ICD-11 will now also include peripheral and central neuropathic pain (Scholz et al. 2019).

The new classifications do not guarantee, consensus in relation to defining chronic, non-malignant pain (Treede et al. 2015; Raffaeli and Arnaudo 2017). Indeed, over recent times, even the use of ‘chronic’ has been called into question and oftentimes, ‘persistent pain’ will be used as an alternative term (Gureje et al. 1998). Discussion over many years has also questioned whether acute and chronic pain can be differentiated by degrees of ‘interference’ with functioning (Grichnik and Ferrante 1991; Schofferman 2006; Nugraha et al. 2019). However,

insufficient agreement on the assessment of interference has been reached and it is accepted that pain of any duration can have a marked impact on a person's ability to continue activities of daily life for the time it is experienced and is not singular to chronic pain (Jennings et al. 2009; Turk et al. 2016; Hayhurst et al. 2018).

From a research perspective, defining chronic non-malignant pain can be inconsistent and can lead to discrepancies in literature, when different classifications are used (Fayaz et al. 2016). Chronic pain as an all-encompassing definition is less commonly used than specific complaints, which may have ongoing pain as a major symptom. Lower back pain for example, would appear more straightforward to recruit for trials and research purposes (Reddy et al. 2012). However, even the area considered to be the lower back differs between studies and whether pain is associated with reduction in activity also (Buchbinder et al. 2013). This has led to authors developing their own definitions for pain and severity and propose them to be used to guide future research (Buchbinder et al. 2013; Hoy et al. 2014).

Pain can be a symptom of disease or injury or considered a condition in its own right (Nicholas et al. 2019; Perrot et al. 2019). Pain is a complex condition, which, despite efforts to better define it, remains contentious diagnostically, particularly when it becomes chronic or persistent. Importantly, pain is a ubiquitous experience and so, has potentially far-reaching consequences for global health.

1.4 Global burden of pain

The Global Burden of Disease study (GBD) is an international project, collecting data from more than 200 countries worldwide. It tracks and examines data from 1990 to the present to provide insight into risk factors and disease prevalence, then used to develop national and international policy and initiatives to improve health and wellbeing of the world's population (Institute for Health Metrics and Evaluation 2020). Over the duration the GBD has been running, there has been a noticeable shift in the number of chronic, long-term, non-communicable

conditions contributing to the overall burden, one measure of which is disability adjusted life years (DALYs). It was reported from the GBD 2019, the burden of HIV/AIDS had substantially dropped since 2004 due to global availability of anti-retroviral drugs (Vos et al. 2020). Headache disorders in people aged 25-49 years increased from rank 7 based on DALYs (3.1% of DALYs) in 2009 to rank 5 (3.7% of DALYs) in 2019 (Vos et al. 2020). Initially, the distribution was weighted more toward communicable diseases (Vos et al. 2020). Rice, Smith and Blyth (2016) explained the change is partly due to changing demographics in developing and developed countries. Populations are becoming older, more obese and less active. All of which contributes to long-term conditions such as type-2 diabetes, which, may also pertain to pain (Rice et al. 2016). In developing countries, there are increasing numbers of road traffic accidents, and road injuries have remained the number 1 cause of DALYs since 2009 for people aged between 10 and 49 years old worldwide (Vos et al. 2020). Road injuries are also associated with pain and possible persistence of it over time (Rice et al. 2016) although this is not necessarily captured in the GBD. Also, rurality and manual working, being more common in low- and middle-income countries (LMIC), is likely to lead to higher incidence of injury and consequently pain. Aging populations and the continued presences communicable diseases such as HIV/AIDs and herpes zoster, also contribute to a neuropathic pain burden (Blyth 2018; Sharma et al. 2019). However, low personal income and poor accessibility to healthcare affects the actions people in LMICs can take, even when they have pain. Access to opioids is limited for example, with up to 80% of world consumption in high income countries, predominantly North America (Sharma et al. 2019; Richards et al. 2020).

Using years lived with disability (YLDs) as the measure, taking account of prevalence and severity of disease, usefully demonstrates the rising burden of long-term conditions in a generally aging global population. Simply put, whilst life expectancy has increased worldwide, it has not been mirrored by longer time spent in good health (Rice et al. 2016). As improvements continue to be made in the treatment of infectious conditions, the rise in long-term, pain-associated

conditions will likely continue unless global policy is developed to address it (Rice et al. 2016; Blyth et al. 2019).

The GBD 2010, reported in 2014 (Hoy et al. 2014) revealed low back pain to be the number one cause of disability worldwide and ranked 12th of the common chronic conditions examined. Whilst ranked first for YLDs it was also ranked 6th for DALYs. Low back pain is established as a major health and economic issue in the UK and other developed countries (Lambeek et al. 2011; Hong et al. 2013) with lifetime prevalence estimated between 51% to 84% (Henschke et al. 2015). The GBD 2010 was perhaps the first acknowledgment that low back pain had become a global health issue with large, reported increases in prevalence in developing nations (Hoy et al. 2014a). In part, this was as likely due to advances in data collection globally, as to a major change in pathology. The status of low back pain as the leading cause of YLDs worldwide was confirmed in the 2017 GBD. An estimated increase of 53% (from 377.5million in 1990 to 577.0 million in 2017) in point prevalence was made for the 27 years, the study examines (Wu et al. 2020). Low back pain was specified the cause of age standardised YLDs for men in 133 of 195 countries and for women in 109 countries in the 2016 study (Blyth and Schneider 2018). In the 2019 GBD, low back pain was ranked 7th and accounted for 3.2% of DALYs worldwide for people aged 10 – 24 years (Vos et al. 2020), further illustrating it to be a condition with a significant and potentially lasting impact.

It is not just low back pain contributing to global pain burden, however. In the 2010 study, the most commonly occurring symptomatic chronic condition was recurrent tension-type headache (Rice et al. 2016). Musculoskeletal pain, which includes at least 150 discrete diagnoses including gout, rheumatoid arthritis, hip and knee osteoarthritis and back and neck pain is also examined as part of the GBD (Blyth et al. 2019). 'Other' musculoskeletal and osteoarthritis were listed in the top 25 conditions for people aged over 50 years in 2019 (Vos et al. 2020), which could be assumed to have pain as a symptom. Falls were the number 8 cause of global DALYs in 2019 for people aged 75 years and over and ranked 16th

for the 50 – 74 years age-group (Vos et al. 2020). The contribution of falls to the experience of pain, is not included however, and herein lies a point of debate, in terms of estimating the true burden of pain, locally or globally (Rice et al. 2016; Blyth and Schneider 2018; Blyth et al. 2019). Given the methodology used to collect and analyse data on a global scale, including navigating various standards of healthcare services and efficiencies of data collection, it is inevitable prevalence figures are in fact an underestimate (Blyth and Schneider 2018). Further, there is a range of conditions for which pain might be experienced and yet, not recorded as part of the study (Rice et al. 2016).

1.4.1 Prevalence of Chronic Pain in the United Kingdom

The Chief Medical Officer's (England) report in 2009 estimated 5 million people each year develop chronic pain in the United Kingdom (UK) with an anticipated recovery rate of around 66% (Chief Medical Officer of England 2009). The National Pain Audit published in 2012 quoted a figure of 7.8 million people living with chronic pain in the UK (Price et al. 2012). This figure, assumed from previous estimates, including a 2006 European survey of chronic pain which gave a prevalence approximation of 13% (Breivik et al. 2006), relates to people living with moderate to severe levels of pain.

Fayaz et al. (2016) produced an extrapolated estimate of 28 million UK residents living with chronic pain, a figure considerably higher than any previously published and equitable to approximately 43% of the population (Fayaz et al. 2016). In their meta-analysis, only studies pertaining to the UK were included and this limited included studies to nineteen. Less than half of those examined had been designed as prevalence studies. The resulting figure is not, however, markedly different from prevalence estimations (Tsang et al. 2008) of widespread chronic pain. The Fayaz paper differs from previous estimates such as Breivik's of 13% (Breivik et al. 2006), gained through direct questioning of people living with pain, by moving the focus away from moderate to severe pain levels, to data relating to chronic, non-cancer pain of any severity.

The Health Survey for England 2017 examined chronic pain. Results revealed a 34% prevalence of pain lasting for more than 3 months, in just under 8,000 people aged 16 years and over (England 2017). A similar prevalence was reported in Ireland (35.5% community prevalence of chronic pain) (Raftery et al. 2011). There was an increase in pain reporting with advancing age and women were disproportionality represented in all age-groups. Pain prevalence exceeded the national average for all adults, at age 45 -54 years, when pain was reported by 39% of respondents (England 2017).

Racial disparities have been noted in pain reporting in the UK and elsewhere (Jimenez et al. 2011; Janevic et al. 2017; Public Health England 2017). In England, black people had an estimated chronic pain prevalence of 44%, when the average for all ethnicities was 34% (Public Health England 2017). As highlighted by Rice and colleagues (2016), chronic pain reporting becomes more prevalent with increasing levels of obesity and low physical activity (Rice et al. 2016). Healthy weight was associated with 29% chronic pain prevalence compared to 54% in people identified as very obese (Public Health England 2017). Less than 30 minutes per week of moderate or vigorous activity resulted in a 14% difference in pain prevalence reporting, compared to those who exceeded 30 minutes (45% compared to 31% respectively) (Public Health England 2017).

1.4.2 The situation in Wales

No studies have to date examined chronic pain prevalence in Wales alone. Fayaz (2016) estimated UK prevalence to be around 44%, based on a systematic review of 19 UK-based studied (Fayaz et al. 2016). Based on a population of 3.2 million (StatsWales 2021) this could mean up to 1.3million people may live with chronic pain in Wales.

Wales is known to have poor levels of general health (Public Health Wales Observatory 2020). Data from StatsWales (StatsWales 2020) on general health and illness in the Welsh population 2017-18 stated that 70% of people aged 16 years or over had good or very good general health. Ten percent of the adult

population were listed as having bad or very bad health (StatsWales 2020). Data for England are presented differently. The last comparative data for England and Wales were released in 2013 (Office for National Statistics 2013) and presented findings from 2011. Then, just over 81% of people in Wales and England reported 'very good' or 'good' general health. Wales and the North East of England had the lowest levels of people rating their health in the higher categories. Blaenau Gwent local authority in Wales had the lowest percentage (72.6%) of people who reported their general health and wellbeing in the top two classifications, which was over 15% lower than the authority with the highest ranking (Hart in Hampshire, 88.1%) (Office for National Statistics 2013). It would appear that, since 2015, general health and wellbeing in Wales has deteriorated.

Musculoskeletal (MSK) complaints account for the highest reported percentage of illness type in Wales. Between 2016 and 2018, the proportion of people affected with MSK conditions remained at 17% (StatsWales 2020). Mental Health disorders affected 8-9% of people aged 16 years and over in the same period of time (StatsWales 2020). Whilst these data do not, on their own, explain the 44% estimate of the population living with pain, it begins to build a picture of the Welsh population and the complexity of collecting and interpreting data about population health.

1.4.3 Economic burden of pain

The impact of pain is far-reaching, going well beyond healthcare systems. The socioeconomic burden is probably higher than for many other health conditions. Pain is often accompanied by poor mental health, high rates of absenteeism and reduced productivity (Phillips and Harper 2011; Henschke et al. 2015). Pain also impacts on more than the individual, posing a significant challenge for families, carers, employers and therefore society as a whole (Latham and Davis 1994; Phillips and Harper 2011; Henschke et al. 2015). High levels of disability are associated with pain (Section 1.4) which is a major influence on the economics of the condition (Phillips 2008).

The economic burden of chronic pain has been estimated at 3 to 10% of gross domestic product in Europe (Breivik et al. 2013), which in 2015 would have been approximately €441 to €1,471 billion per year (~£381 to £1,273 billion) (Bourgeais and Krueger 2017). Estimates from the USA, based on 100 million people experiencing pain of any level, were calculated between $560 and $635 billion annually (Richard and Richard 2012). In Australia, with a population of 22.7 million people, total costs of pain in 2007 were $34.3billion (~£19billion). As illustrated by the GBD study (Section 1.4), pain is a major burden globally, although estimates of subsequent costs from developing countries are more difficult to determine. More specifically, a UK estimate for back pain was made for over £10billion, based on a prevalence of between 36% and 37% (age range 16+ years, 47 million population) (Maniadakis and Gray 2000). A similar study in Germany estimated total costs of back pain to be €48.96 billion (~£42billion) (age 18 years and over, 61.8 million population) (Wenig et al. 2009). The UK total included an estimate of £140.6million spent in primary care services such as general practice and home care, which, accounted for 13% of NHS costs although only 1-2% of the full economic cost estimate. Employment costs lost due to low back pain, were 5 to 10 times that of NHS healthcare (Maniadakis and Gray 2000).

As with disease burden, the full economic consequences of pain are likely to remain underestimated. This is in part due to its ubiquitous presentation as a symptom of other conditions, but also as the consequences of living with chronic pain are far-reaching and can be difficult to quantify.

1.5 Pain management in general

The multiple definitions of pain (Section 1.2) result in a variety of approaches to treating or managing it. It has been acknowledged for years, that pain, whilst felt physically, is a complex perception, influenced by more than physical change or injury (Eccleston 2001; Nicholas et al. 2019). In 1997, Gifford and Butler acknowledged that acute and chronic pain were not simple mechanisms but influenced by components including nociception, central processing (including

how the brain modifies the response to incoming stimulation) and motor and autonomic responses. They highlighted that pain is an 'experience' and as such an individual's emotions and previous encounters with pain influence their presentation at any time (Gifford and Butler 1997). Moseley (2007) proposed that pain intensity is not related to tissue damage. The longer pain persists, the less predictable the relationship between tissues and pain becomes (Moseley 2007) implying a crossover between acute and chronic pain experiences, with the balance of biological and social or psychological influence varying with the individual and time.

Brena and Sanders (1992) were amongst the first to widen the desirable outcomes of chronic pain management beyond only a reduction in painful sensation. In addition to reduced discomfort, they listed the needs of people suffering chronic, non-cancer pain as increasing function, lifestyle improvements, reduced environmental stress and returning to work (Brena and Sanders 1992). Clearly, many of these factors will not be resolved by medicines. Recent pain-related guidelines from the National Institute for Health and Care Excellence (NICE) have been careful to stress the importance of taking into consideration the individual's experience, level of distress in addition to their physical debilitation (National Institute for Health and Care Excellence 2016; National Institute for Health and Care Excellence 2021). The Scottish Intercollegiate Guideline Network (SIGN) also promotes a holistic approach to management. As with NICE, SIGN promotes the offer of non-pharmacological strategies such as psychological support, increasing activity and addressing social concerns such as relationships and employment before medicines and especially opioids, are initiated (Scottish Intercollegiate Guideline Network 2019).

NICE recently faced criticism for reducing the number of medicines recommended for use in chronic primary pain (Eccleston et al. 2021; Smith et al. 2021), which includes conditions such as fibromyalgia and complex regional pain syndrome (CRPS). Although medicines are less commonly promoted as first line options for managing chronic, non-cancer pain conditions, they remain an

important component of pain treatment regimens for some people. For example, low back pain may be helped by the use of non-steroidal anti-inflammatory medicines such as ibuprofen and naproxen (National Institute for Health and Care Excellence 2016; Scottish Intercollegiate Guideline Network 2019) and in osteoarthritis, paracetamol and non-steroidal anti-inflammatories are suggested as first line medicine options (National Institute for Health and Care Excellence 2014; Scottish Intercollegiate Guideline Network 2019). Other guidelines such as those from Royal College of Physicians for CRPS (2018) suggest more specific approaches to managing the named condition including the particular specialist services which may benefit the patient at different stages of their treatment (Goebel et al. 2018). There may not always be agreement on the overall approach of guidelines, especially those produced by NICE, which have potential to widely influence practice in the UK and further afield (Eccleston et al. 2021; Smith et al. 2021). However, what an increasing number of guidelines have in common is the suggestion that functional outcomes are more important than pain reduction per se and the promotion of analgesic medicines other than opioids, for the majority of commonly occurring non-cancer pain-related conditions (National Institute for Health and Care Excellence 2016; Scottish Intercollegiate Guideline Network 2019; Stewart et al. 2019; National Institute for Health and Care Excellence 2021).

1.6 Contemporary use of opioids

Opioid analgesics are widely prescribed in Wales and the UK as a whole (Ruscitto et al. 2015; Brinksman 2018; Davies et al. 2018; Curtis et al. 2019). They are acknowledged as effective analgesics (Faculty of Pain Medicine 2021). Opioids have been the mainstay of pain relief for a multitude of conditions for hundreds of years, in one form or another (Meldrum 2003; Sabatowski et al. 2004). Opioid analgesics including morphine are well established to treat pain caused by trauma or surgery and also in the management of pain due to cancer and at the end of life (Faculty of Pain Medicines 2021). It is likely from the history of opioid use, that differentiation of pain-type has not always been a consideration in the use of these drugs (El-Ansary and Galiongy 1984).

1.6.1 Acceptability of opioids in non-cancer pain

Opioid analgesics were not considered a common part of chronic, non-cancer pain management for the majority of the 1900's (Meldrum 2003; Sabatowski et al. 2004). This changed following the publication of a seminal series of case reports by Portenoy and Foley in 1986 (Portenoy and Foley 1986). The authors described 38 cases of chronic non-cancer pain, where opioids were used for extended periods and examined retrospectively. Although morphine equivalence was used to describe the doses used, the patients did not use morphine – twelve receiving oxycodone with others having methadone, levorphanol (not used in the UK), codeine and others regarded as 'weak' opioids. The authors concluded the use of opioids for managing chronic, non-cancer pain could be "*safe, salutary and more humane*" alternative to current methods employed at the time of surgery or no treatment (Portenoy and Foley 1986).

McQuay (1989) focused on practical considerations such as efficacy, ceiling effect and toxicity but ultimately reinforced support for using opioid analgesics for chronic pain (McQuay 1989). In the USA, prescribing laws were relaxed, and liberalization of opioid prescribing led to a rapid escalation in their use (Franklin et al. 2012). The trend was quickly mirrored in other developed nations where rises in prescribing of opioids of all types were observed from the mid 1990's onwards (Ruscitto et al. 2015; Karanges et al. 2016). Opioid prescribing in non-cancer pain was rationalised by statements such as '*there is consensus among pain specialists that opioid therapy is appropriate for selected patients with chronic pain and can provide sustained benefit to such patients*' (Franklin et al. 2012). However, even though more people were being prescribed opioid analgesics, concern was also expressed. Less than 10 years after the Portenoy (1986) paper, Large and Schug questioned whether the use of opioid analgesics for non-cancer pain raised questions about 'the purpose of pain management' (Large and Schug 1995). The authors asked if opioids create self-sufficiency in people living with pain or made difficult lives more limited. Should the aim of

pain management be total pain relief or improved function and quality of life? (Large and Schug 1995).

In the subsequent 25 years, the debate on using opioids for long-term pain management in particular has continued to rage. The idea that pain intensity and therefore, reducing it as the main goal of treatment, was promoted especially in the USA. In 1996, the then President of the American Pain Society proposed pain should be considered the '5th vital sign' (Sullivan and Ballantyne 2016). The result of the initiative was not simply to raise the profile of pain as a condition in its own right. It also gave credence for both patients and practitioners to use analgesic medicines to reduce pain and opioids, so often reported as 'gold standard analgesics' (Bekkering et al. 2011; Wiffen et al. 2017) were the obvious choice to use. Further, the inclusion of pain intensity as an outcome measure is postulated by many, as the reason for the rapid rise in opioid prescribing in America and elsewhere (Franklin et al. 2012; Sullivan and Ballantyne 2016; Todd et al. 2018). Whilst rates of prescribing were increasing across the world, evidence was emerging of rising prescription opioid-related overdoses and deaths (Gomes and Juurlink 2016; Spooner 2016) in North America, leading to what is now referred to as the 'Opioid crisis' (McGreal 2018; Centers for Disease Control and Prevention 2021). Although opioid-related deaths and hospital admissions have increased in UK (Liddell 2019; Turner et al. 2019) only around 8.2% are related to prescription opioids, compared to 40% in the USA (Stannard 2018b). As importantly perhaps, opioid analgesics do not have good evidence of effect for the majority of people who use them (Rivat and Ballantyne 2016; Stannard 2018a; Faculty of Pain Medicine 2021) (Section 1.6.3). The use of opioid analgesics is also associated with significant adverse effects, which, have become better recognised in the last 20 years (Section 1.7).

High pain scores in chronic pain states are often a measure of distress, desire for support, depression and anxiety rather than physical pain per se (Blozik et al. 2009; Sullivan and Ballantyne 2016; Stannard 2018b). Continuing poorly effective medicines, aiming to reduce pain intensity and which do not seem to make life

more bearable for all people living with pain is becoming questionable clinical practice in the UK (Large and Schug 1995; Ballantyne et al. 2016; Stannard 2018b). Despite that, opioid analgesics continue to be frequently prescribed (Curtis et al. 2019; Jani et al. 2020). In the USA, opioid prescribing remains highly politicised and a source of conflict between different clinicians and patient-groups, with starkly drawn views on the place of the medicines in pain management (Matthias et al. 2014; Mackey 2019; Schatman and Shapiro 2019; Matthias 2020; Nichols et al. 2020).

In the UK, discussion tends to be more nuanced. For instance, recently published National Institute for Health and Care Excellence (NICE) guidance for managing chronic primary pain in over 16's, recommended against offering all standard analgesics including opioids (National Institute for Health and Care Excellence (NICE) 2021). Authors have argued that NICE ignored swathes of literature which support commonly used interventions and treatments, leading to only a small number of recommendations for treatment being made (Eccleston et al. 2021; Smith et al. 2021). Whilst pro-analgesic American literature tends to focus on patients' 'right' to opioid analgesics and the expectation pain will be relieved, UK clinicians' focus is on ensuring individualised care, including non-pharmacological support, remains available for those who may benefit from it. In the UK, there is little disagreement with the notion that opioids should not be routinely offered for long-term pain conditions (Centre for Clinical Practice at NICE 2013; National Institute for Health and Care Excellence 2014; National Institute for Health and Care Excellence 2016; National Institute for Health and Care Excellence 2021), signalling perhaps they are becoming less acceptable for long-term pain management.

1.6.2 Arguments in support of opioids

At the point that opioid analgesic use for chronic non-cancer pain became more widespread, little trial data supported their use (Franklin and Neurology 2014; Faculty of Pain Medicine 2021). In the late 1990s, a lack of reasonably conducted clinical studies in chronic, non-cancer pain has been suggested to have allowed

some treatment methods to "*gain a foothold in the mythology of pain management before controlled trials are conducted*" (Justins 1996). It was acknowledged even then that using opioids for chronic non-cancer pain was controversial (Justins 1996). However, patient surveys and case reports were published which supported the use of long-term opioids for nociceptive and neuropathic pain in carefully selected patient groups. It was recognised that people with chronic non-cancer pain would often state a preference for opioids over other medication choices (Collett 2001).

What studies were available, predominantly compared opioids to placebo and used a variety of administration routes including parenteral, where application in clinical practice is limited. The overall conclusions from these early trials demonstrated a reasonable effect of opioids in nociceptive pain although neuropathic pain responded less well and idiopathic pain appeared not to respond to opioids at all; albeit in mostly uncontrolled circumstances and with small patient numbers. (Collett 2001). Similarly, tentative support for using opioids was issued from a Cochrane systematic review and meta-analysis which suggested that "*proper management of a type of strong painkiller (opioids) in well-selected patients with no history of substance addiction or abuse can lead to long-term pain relief for some patients…"* (Noble et al. 2010). The paucity of comparative data with other drug classes such as anti-inflammatories and anti-depressants in studies examining the use of opioids in the management of chronic low back pain was also noted by Chaparro (2013). Where data are available, little difference between opioids and other drugs exists in either efficacy or their effect on functional improvement (Chaparro et al. 2013).

Attempts continue to determine the efficacy of opioids for chronic non-cancer pain compared to other medications as well as placebo. Previously, Furlan et al. (2006) tried to establish whether certain types of chronic non-cancer pain responded better to opioids than others using a systematic review of literature up until 2005 (Furlan et al. 2006). The group examined data on opioids in chronic non-cancer pain using pain for longer than six months as the working definition

of the condition. However, in terms of opioid use, durations greater than 7 days were included which, in chronic pain practice would be an unusually short period of time of use. Data from 41 studies including over six-thousand people, published prior to 2005 were examined for the study. Eighty percent of people included in these studies had diagnoses of chronic nociceptive pain and 12% had neuropathic pain (Furlan et al. 2006). The longest mean length of opioid therapy was just under 9 weeks, which would not be regarded as 'long-term' use in practice. Following meta-analysis of 28 placebo controlled trials the authors conclude the findings were in favour of using opioids in respect of pain relief (Furlan et al. 2006). There was little difference between types of opioids in terms of efficacy.

Further, when compared to other analgesic medicines, including those used for neuropathic pain such as tricyclic anti-depressants, there was little variance in effectiveness for pain relief. The authors highlight inadequacies in the various study designs, which would affect the accuracy of the outcomes reported (Furlan et al. 2006). The majority of studies conducted in this area have included only small patient numbers and were often uncontrolled, which throws doubt on their subsequent findings (Collett 2001). In a later paper, Furlan's group undertook an analysis of a further 4 years of data which added twenty-one trials to the previous study. Head-to-head comparisons of opioids were excluded but they did look at a small number of studies comparing opioids to non-opioid analgesics such as non-steroidal anti-inflammatory drugs. Trials were again short-term, the longest being 24 weeks but the majority less than 6 weeks. Eighty-seven percent of the trials had significant input from pharmaceutical companies, which could further bias the outcomes (Furlan et al. 2011).

Overall, it appears opioids can provide reduction in pain levels for a small number of people for a relatively short period of time. The current evidence does not however, demonstrate that opioids can provide long-term pain relief or functional improvement (FAHMS et al. 2016, Häuser et al. 2021). High quality, long-term studies which are better able to identify which patient groups and

conditions are most likely to benefit, are needed (Noble et al. 2010; Franklin and American Association of Neurology 2014).

1.6.3 Are opioids effective in all types of pain?

Commonly, discussions about the place of opioids state, "*Opioids are very good analgesics for acute pain and for pain at the end of life but there is little evidence that they are helpful for long term pain"* (Faculty of Pain Medicine 2021). However, this statement is not unequivocally borne out in the literature (Wiffen et al. 2017). There is a suggestion morphine and fentanyl may be more effective than other opioids in cancer pain although the evidence-base is perhaps, not as strong as perceived by most clinicians who commonly prescribe them in practice (Wiffen et al. 2017). A similar issue pervades acute pain management, where evidence of widespread opioid use has possibly been perceived as evidence of effectiveness (Schug et al. 2016). Currently therefore, opioids maintain an important and for many, useful part of their pain management regimens for acute pain and pain associated with cancer and end of life. Importantly, clinical practitioners and prescribers are familiar with using them.

Mounting interest in short-term prescribing becoming long-term use and the subsequent implications of it, have led to different approaches being advocated. Avoiding modified-release opioids and using multi-modal treatment for post-operative pain has been suggested as a means of reducing chronic use (Levy et al. 2021). Consideration of long-term opioid harms in cancer pain is increasingly important, particularly as more people are surviving or living for longer with the disease (Ballantyne 2003; Jones et al. 2020). Perhaps more so than with other pain types, it is generally acknowledged, in the UK, Europe and Australia at least, evidence to support the use of opioids in chronic, non-cancer pain is limited (Hansen et al. 2015; FAHMS et al. 2016). In North America, it seems lines are drawn between professional and patient groups with differing views of the place of opioids in chronic pain management. Advocates of opioid use are noted to refer to their 'rivals' as 'opioid zealots' and claim they are working to deny people with pain effective treatment (Schatman et al. 2016; Oliver and Carlson

2020). Those labelled ‘zealots’ would claim to advocate a harm reduction approach to opioid use (Kolodny and Frieden 2017).

Theories abound as to the reasons behind the apparent lack of efficacy of opioids in chronic non-cancer pain (Chou et al. 2009; Chapman et al. 2010; Faculty of Pain Medicine 2021). Possible explanations include tolerance, whereby increasing doses of the drug are required to illicit the same analgesic effect, opioid-induced hyperalgesia and even loss of placebo effect with prolonged use (Ballantyne and Shin 2008). Concerns about the association of long-term opioid use and higher rates of impairment including misuse and dependence are often quoted in guidelines as a reason to avoid using them for extended periods of time (Franklin and American Academy of Neurology 2014; Dowell et al. 2016). There is limited data on the prevalence of chronic opioid use in individuals in the UK, however, Bedson (2016) demonstrated of people receiving opioids for periods greater than 2 years, the percentage prescribed long-acting controlled opioids increased from 3.5% to 22.6% between 2004 and 2013 (Bedson et al. 2016). Jani et al. (2020) observed 14.6% (n=1,968,742) of people newly started on opioid analgesics, became long-term users within the first year, albeit long-term in this instance was receipt of 3 prescriptions in 90 days (Jani et al. 2020). Increases in long-term opioid analgesic prescribing has been observed outside of the UK as well. In an Australian cohort (n=1,936,573) long-term opioid prescribing prevalence increased from 5.5% in 2012 to 9.1% in 2018 (Black-Tiong et al. 2021).

1.6.4 Why are opioids prescribed?

Prescribing opioids has been suggested to be a surrogate for access to alternative pain management support (Finestone et al. 2016). Pain service provision in Wales was not mapped as part of this study but, the National Pain Audit (2012) collected data demonstrating every health board in Wales had chronic pain service provision, with 80% claiming to have multi-disciplinary teams which, as a minimum would compose a medical doctor, physiotherapist and psychologist (Price et al. 2012). Average waiting time for those services at the time of the

audit was 33 weeks (Price et al. 2012). Official figures on waiting times for pain services were not available, during the composition of this thesis, although it is acknowledged post-Covid 19-pandemic, waiting times will have increased substantially.

The Royal College of General Practice's (RCGP) guidance to its members is to continue to offer support and treatment to people, even if they are waiting for or receiving input from specialist providers. This may lead to GPs and other practitioners in primary care, resorting to prescribing opioids or maintaining them in the face of poor outcomes, simply because they feel they have nothing else to offer (Finestone et al. 2016).

McCrorie's (2015) study supported this notion, with GPs explaining during interviews, that continuing to prescribe opioids was often due to long waits for other treatments or support or patient's not being ready to consider alternatives to medicines (McCrorie et al. 2015). An examination of routinely collected, longitudinal data from primary care practices in England, noted increasing numbers of primary care appointments were more likely to result in the prescription of a strong opioid. An odds ratio (OR) of 3.04 (range 2.48 – 3.73) where there were more than 12 visits per year was observed (Foy et al. 2016).

The same study demonstrated referral to chronic pain services also resulted in an increased likelihood of strong opioid prescribing that was also more likely to persist (OR 5.74, range 5.09-6.47) (Foy et al. 2016). Something commonly heard in practise, was also reported in McCrorie's study, *"...every time I send somebody to chronic pain [clinic] they come out with more medication, or injections.' [GP, female; Leeds; 319]"* (McCrorie et al. 2015). If this is the case, then whilst prescribing sits predominantly in primary care (Curtis and Goldacre 2018) it would seem influences on prescribing could be greater than simply 'prescriber preference' or lack of alternative.

1.7 Adverse effects of opioids

Opioids are associated with an array of adverse effects (Breivik and Stubhaug 2014), a number of which have historically been considered less clinically relevant when the drugs are only being used for a short period of time, when a potentially life-threatening condition is causing pain or at the end of life. Commonly cited adverse effects of opioids in clinical trials are constipation, nausea and vomiting, dizziness and drowsiness (Furlan et al. 2006).

Studies have demonstrated correlation with endocrine dysfunction (Katz and Mazer 2009) increased risk of falls and fractures on older people (Baldini et al. 2012), sleep-disordered breathing (Baldini et al. 2012; Els et al. 2017), neonatal abstinence syndrome (Desai et al. 2015), cardiac issues e.g. QT prolongation with methadone (Everdingen et al. 2013), opioid-induced hyperalgesia (Higgins et al. 2019; Faculty of Pain Medicine 2020), non-fatal overdose (Brady et al. 2017; Holloway et al. 2018), increased number of emergency department visits (Braden et al. 2010; Nelson et al. 2015), death from unintentional poisoning (Coyle et al. 2018; Alho et al. 2020).

The wide-ranging effects and generic nature of adverse effects, many of which can be experienced by people with long-term pain or linked to co-morbid conditions, is likely to result in opioids being initially at least, overlooked as causative in their presentation.

1.7.1 Effects associated with duration of opioid use

Taking opioid analgesics for longer periods of time, have been associated with a number of negative health outcomes (Jain et al. 2018). There is limited evidence a minority of people remaining on opioids for more than 6 months, experience a persistent reduction in pain intensity (Noble et al. 2008; Faculty of Pain Medicine 2021 In one study, 50% of people remaining on opioids for up to 10 years continued to report severe to unbearable pain (Jensen et al. 2006). This was followed by another study showing doses above 30mg oral morphine equivalent (OMEQ) dose for more than 1 year were associated with higher stimulated pain

intensity than observed in non-opioid users or those receiving lower doses. Baseline pain levels were higher in people on long-term opioids as well (Cohen et al. 2008).

Use of opioid analgesics have been associated with lower quality of life (Jensen et al. 2006). A study of chronic pain in Denmark, observed 60% of people discharged from pain clinic on modified release opioids, remained on them 10 years later. Whilst dose reduction was as common as dose increase over that time, depression recurred or emerged in nearly 30% of opioid users and quality of life measures were statistically lower compared to non-users (Jain et al. 2018). Corroborating earlier findings of the risk of new-onset depression being 18% in people using opioids for 30 - 90 days, rising to 35% increased risk with more than 90 days use (Scherrer et al. 2016). The dose of opioid was not significantly associated with depression onset, which, as with Jain's (2018) findings, is suggestive that duration of use is a more important factor.

People using opioid analgesics for more than 6 months prior to undergoing spinal surgery were nearly 40% more likely to develop wound infections and just over 20% more likely to have the procedure repeated within a year(Jain et al. 2018).

1.7.2 Quality of life

Living with pain takes a huge toll on individual's quality of life (QoL) (Smith and Torrance 2012; Husky et al. 2018). Using opioid analgesics was assumed would lead to reduced levels of pain and consequently, improve all other aspects of a person's experience (Portenoy and Foley 1986; Trescot et al. 2008). A 2005 systematic review, funded by the Janssen-Cilag pharmaceutical company, reported improvements in pain and QoL for people using a range of opioid analgesics with doses of up to 1.2g OMEQ per day, 10 times the now recommended maximum 120mg OMEQ dose for chronic pain (Faculty of Pain Medicine 2021). On closer examination however, only 4 of 11 studies included could provide evidence of an improvement in QoL scores, following up to 2 years treatment with opioid analgesics. One of those 4, assumed improvement in

physical function correlated to improved QoL (Devulder et al. 2005). An optimum dose of around 40mg OMEQ per day has been suggested, in terms providing physical or functional improvement, reduce pain intensity and increase overall well-being. High doses of opioids are associated with initial increases in feelings of well-being and quality of life, but this does not appear sustained (Dillie et al. 2008; Els et al. 2017)

Since 2005, there has been substantial change in the focus of pain management, from being aimed predominantly at reducing pain intensity to focusing on function and quality of life (Hanna 2012; Rice et al. 2016; Merriwether et al. 2018; Stilwell and Harman 2019; NICE 2020). Further, as time goes on, evidence continues to emerge of the detriment opioid analgesics can inflict on quality of life (Dillie et al. 2008; Baldini et al. 2012; Els et al. 2017; Solà et al. 2019). A sample of people in primary care living with chronic pain, demonstrated significantly lower health related QoL scores with doses of opioids greater than 105mg OMEQ (Dillie et al. 2008).

It is important to note, for a minority of people, who are able to tolerate any adverse effects that occur, there is a small amount of evidence opioids can be helpful to maintain pain levels at a manageable level, thus facilitating improved function and quality of life (Noble et al. 2008; Faculty of Pain Medicine 2021).

1.8 Gender differences in pain

Epidemiological and clinical studies have consistently, but not exclusively, reported women to have a higher prevalence of painful conditions and to experience higher levels of pain than men (Fullerton et al. 2018; Dance 2019). Differences between male and females have been acknowledged for many years, yet a review in 2005 highlighted 79% of animal studies published in the preceding 10 years in a leading research journal, had only included male subjects. Only 4% of published work had examined gender differences (Mogil and Chanda 2005).

Why do differences exist? It may not be possible to fully elucidate the answer due to the complexity of pain, particularly chronic pain and the numerous facets that impact upon pain perception. However, potential theories for gender differences in pain and analgesic response have been put forward (Fullerton et al. 2018). Most obvious is steroid hormone differences between male and female subjects, including changes depending on the stage of menstrual cycle or whether female subjects are pre- or post-menopause (Greenspan et al. 2007). Observed differences in pain symptoms between sexes, in the period after puberty and before menopause are highly suggestive that sex steroid hormones have a role in the experience of pain (Sullivan et al. 2000; LeResche et al. 2005; Vincent and Tracey 2008). Testosterone, which after puberty is significantly higher in males than females, has been postulated to be protective, and may have an analgesic role based on findings in particular painful conditions such as temporomandibular joint pain (Fischer et al. 2007; Vincent and Tracey 2008). These findings are supported by studies demonstrating reduced androgens in men and women with rheumatoid arthritis, where exogenous androgen improve pain symptoms in both sexes (Vincent and Tracey 2008). Differences are not seen in all pain modalities however (Ruau et al. 2012; Sorge and Strath 2018), highlighting it is too simplistic to assume sex hormones are the only explanation.

Emotional differences have also been suggested as a possible explanation for some observed differences (Rhudy and Williams 2005; Coll et al. 2012). Women tend to be more reactive to negative stimuli and perceived threat (Rhudy and Williams 2005). This might even include the extent to which pain in perceived in others, based on the perceived threat to the person being observed (Coll et al. 2012). Emotional responses such as frustration, depression and anxiety have been observed to have different effects on men and women's pain experience. For example, pain intensity was heightened by feelings of frustration in women, but by depression and anxiety in men, in one study (Riley et al. 2001). Catastrophic thinking, where experiencing pain is associated with rumination on worst case outcomes, appears to occur more frequently in women than men and is associated with greater pain reporting (Keefe et al. 2000; Sullivan et al. 2000),

adding weight to the emotional component of pain being an important consideration when assessing and supporting men and women in pain.

Sex differences have also been shown in the response to opioid analgesics (Fillingim and Gear 2004; Niesters et al. 2010; Pieretti et al. 2016; Fullerton et al. 2018). Animal experimental models have shown sex differences in opioid responses, which are seemingly reversed in humans i.e., male rats have a more robust response than females, yet female humans appear to respond better to opioids (Fillingim and Gear 2004). A systematic review found women to be more responsive to parenteral morphine, but no sex differences in response to other forms of opioids (Niesters et al. 2010). Other studies have not shown analgesic differences but have demonstrated women to be more susceptible to adverse effects (Fillingim et al. 2005; Fullerton et al. 2018). Sex differences in metabolic pathways and inter- and intracellular mechanisms by which opioids take their effects have been put forward as contributing to the variation in response that is noted clinically (Fullerton et al. 2018).

1.9 Does age impact on pain?

It is no secret the population of the UK is getting older. Estimates suggest people age over 65 years will comprise to 36% of the UK population by 2050 (Schofield 2017a). Frequency of pain has been shown to increase with age up to around the sixth or seventh decade, at which point it appears to plateau or decrease (Molton and Terrill 2014).

Age in itself is not painful. There should be no assumption that pain is 'just part of getting older'. However, getting older brings with it a greater tendency to develop problems which can impact on quality of life and so increase the likelihood of experiencing pain (Gibson and Helme 2001; Gibson and Farrell 2004; Docking et al. 2011; Gibson and Lussier 2012). Functional disability reduced social and support networks and higher disease burden have all been associated with higher pain prevalence at any age but are more common as people get older (Gibson and Helme 2001; Schofield 2012). Pain prevalence has

been reported as 73% for older people living independently and rising to 80% if living in a care home (Schofield 2012).

As with gender differences in pain, the reasons for changing perceptions of pain with aging are multifarious. Changes in brain connectivity are shown to increase pain threshold and increase pain intensity in older people (age 60-79 years) compared to younger people (age 18-26 years). In the experiments described pain in older folk appeared to be increased in due to a reduction in descending inhibition, a process which normally tempers intensity (González-Rolḑan et al. 2020). The findings corroborated previous studies where pain perception was demonstrably altered in older people, by later activation and reduced inhibition resulting in a more intense perception (Marouf et al. 2014; Lautenbacher et al. 2017).

Other factors impacting pain experience in older people includes limited physical function, possibly due to pain but which can also further exacerbate it (Schofield 2012; Molton and Terrill 2014). Sleep disturbance is common in people living with pain (Lusa et al. 2015) but has been reported twice as often in older people with chronic pain (Molton and Terrill 2014). High impact pain, where pain intensity is reportedly low but functional impact and low mood is significant is found in around 25% of older people with pain (Corran et al. 1997). This is considered due to the greater impact of co-morbidities on mood and function in older people, which has a consequent effect on the individual's perception of pain (Gibson and Lussier 2012; Aguera-Ortiz et al. 2013).

Depression also links to dementia, which itself is a growing concern within an aging population. Pain assessment is difficult to undertake with people who are living with cognitive impairment or communication problems which may result in pain going untreated if it is misdiagnosed as agitation for example (Schofield and Abdulla 2018). Depression and early symptoms of cognitive impairment can be tricky to distinguish in clinical practise but if left unsupported, both can worsen the experience of pain in the individual (Zis et al. 2017).

Another consideration for older people, is how analgesics fit into this picture. Polypharmacy appears to increase with age. In Wales, it was demonstrated that nearly a third of registered patients aged over 74 were prescribed at least 10 medicines in primary care (All Wales Medicines Strategy Group 2014). Opioids have a range of interactions with other medicines commonly prescribed in older people, such as sedative hypnotics (All Wales Medicines Strategy Group 2014). Side-effects from opioids are exceedingly common and increase in likelihood with age due to changes in drug handling e.g., reduced elimination due to renal insufficiency (Pergolizzi et al. 2017). Adverse effects including nausea, vomiting and constipation (BNF: British National Formulary - NICE. 2021) but also sedation (Tan et al. 2015), depression and anxiety (Mazereeuw et al. 2018), osteoporosis, falls and fractures (Katz and Mazer 2009) which are already more prevalent in older people (Stubbs et al. 2014a; Stubbs et al. 2014b), thus potentially worsening overall health and wellbeing. Concerns about harms of opioids have to be balanced against the risks of undertreating pain which has also been reported as more common in older people (Schofield 2017b). Prescribers report concern when issuing opioids for older people, not least due to fear of causing harm due to dose or interactions (O'Brien and Wand 2020). No evidence has been found to suggest opioids are more or less effective in older than younger people. However, considerations about the risks and benefits of prescribing opioid analgesics to older people need to be made in an individual context, taking account of a wide range of factors as described.

There is no previous research available from Wales, that has examined opioid prescribing trends, or has analysed whether gender or age differences exist in opioid use, outside of illicit drugs (Holloway et al. 2018; Walsh and NWIS 2019). Considering the evidence for using opioid analgesics and effects of gender and age on the experience of pain, does not on its own, explain why opioids are prescribed on an individual or population basis. Rather it is part of setting the context in which prescribing trends were formed.

1.10 Inequality and deprivation

"*Inequality kills slowly, gently, just a small additional effect every day.*" (p.1, Bambra 2016). This, written by Danny Dorling in Clare Bambra's book 'Health Divides: Where you live can kill you' (Bambra 2016), echoes the sentiment expressed in reports examining social determinants of health in the UK (Marmot & Bell 2012; Marmot 2017). Connections between poor health, including drug misuse and deprivation are not disputed (Marmot 2005; Liddell 2019; Taylor et al. 2019). It is also acknowledged that pain is more prevalent in areas of poverty (Todd et al. 2018; Moore et al. 2020). Socio-economic deprivation is significant in the UK. It was estimated up to 1.5million people were destitute at some time in 2017 (Unit 2013). In-work poverty has risen faster than employment, resulting in around a fifth of the UK population being classified as 'poor' (Barnard 2018). The coronavirus pandemic has resulted in heightened recognition of poverty within the UK population and the subsequent health divides that result (Whitehead et al. 2021)

The Joseph Rowntree Foundation highlight four areas of industry which have high rates of in-work poverty: accommodation and food services; agriculture, forestry and fishing; administrative and support services; and wholesale and retail (Joseph Rowntree Foundation 2017).These areas now form the basis of the Welsh economy since the decline of heavy industry, including coal-mining (Welsh Government 2016).

Differences exist between the four nations of the UK but also within each country (Bambra 2016; Joseph Rowntree Foundation 2017). Wales has maintained higher prevalence of poverty than England, Scotland or Northern Ireland since the late 1990's despite a small reduction in the percentage of population affected (Barnard 2018). Comparing rates of deprivation between the four nations is not as straightforward as it might appear, given each publishes indices of deprivation (Welsh Government 2011) undefined. Deprivation domains vary between countries (Table 1.1) and are subject to change. Welsh indices were updated in 2019, with component domains changing percentage

contribution to the overall score (Welsh Government 2011). It has been suggested these differences, albeit small, may result in misleading outcomes (Abel et al. 2016). Differences in mortality rates appeared worse in Wales compared to England when using each country's own indices of deprivation, with the gap closing when a common schema was used (Abel et al. 2016). International comparisons can be further complicated by differences in welfare and regulatory systems (McAreavey & Brown 2019), as well as cultural and social variances (Guillaume et al. 2016).

Table 1.1: Comparison of domains used to develop indices of deprivation for each country in the United Kingdom

Domain	**Percentage of each domain for final deprivation score (%)**			
	Wales	Scotland	Northern Ireland	England
Income	23.5	28	25	22.5
Employment	23.5	28	25	22.5
Education	14	14	15	13.5
Health	14	14	15	13.5
Crime / community safety	5	5	5	9.3
Barriers to housing/services	-	-	-	9.3
Housing	5	2	-	-
Access to services	10	9	10	-
Living environment	5	-	5	9.3

(Welsh Government 2011; Northern Ireland Statistics Research Agency 2017; Ministry of Housing 2019; National Records of Scotland 2020)

Whilst levels of poverty are higher in Wales than elsewhere in the UK, Scotland is said to have worse health outcomes and lower life-expectancy than the other home nations (Whynes 2008; Bevan et al. 2014; Bambra 2016). Other measures however, such as waiting times for surgery are generally lower in Scotland and England, with Wales and Northern Ireland consistently reporting much longer waits (Sutherland & Coyle 2009; Bevan et al. 2014) which may then be associated with greater debilitation and potentially poorer outcomes.

Julian Tudor-Hart, a general practitioner working in the South Wales Valleys, published his seminal work, 'The Inverse Care Law' in 1971 (Tudor Hart 1971). It is as valid now, as it was when written, 23 years after the establishment of the National Health Service (NHS). An ideal of the NHS, declared by Nye Bevan "….*to generalise the best health advice and treatment"* (Delamothe 2008) was based on the intent for all people, regardless of circumstance, to receive the same

service dependent on need, rather than the ability to pay. As Tudor-Hart highlighted, despite the best efforts of those working in the NHS, *"The availability of good medical care tends to vary inversely with the need for it, in the population served"* (Tudor Hart 1971).

Whilst NHS services are free at the point of delivery and available throughout Wales, there remains inequitable access to services, with some areas of overall low deprivation, being poorly served by medical and other public services (Figure 1.2 Comparison of Welsh Index of Multiple Deprivation domains, contrasting health (left)).

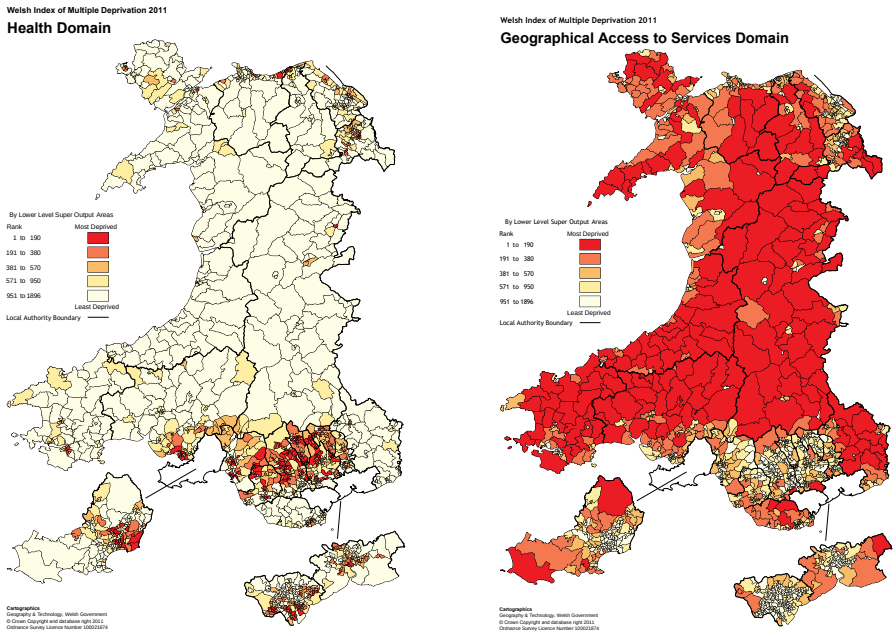


Figure 1.2 Comparison of Welsh Index of Multiple Deprivation domains, contrasting health (left) with geographical access to services (right) using the 2011 WIMD (darker colours = more deprived) (Welsh Government 2011)

1.10.1 Determinants of health in the Welsh population?

The areas of Wales with the greatest levels of deprivation now, are concentrated in the old coalfields such as the Rhondda and Merthyr valleys, Caerphilly, and Blaenau Gwent in the South, Flintshire in the North and Pembrokeshire in the West. The legacy of unemployment and lack of investment can be seen when travelling through those areas. "Worklessness' has been associated with 3 times

higher reporting of ill health than areas with high employment (Del Roy Fletcher 2007). Direct links between social inequalities and health inequalities have been made and demonstrated time and again (Whynes 2008; Marmot & Bell 2012; Galama & van Kippersluis 2019). However, it is a likely over-simplification that economic deprivation alone is the cause of poor health. Levels of health are often worse than would be predicted by the level of deprivation alone (Whynes 2008). Referred to as the 'Scottish effect', as it was first described in that population, but has subsequently been demonstrated in English and Welsh populations (Whynes 2008).

Since the late 1990's social determinants of health have been considered more in policy formation than deprivation alone (Marmot 2005; Public Health England 2017; Welsh Government 2017). Social determinants of health are broadly defined as, '*the conditions in which people are born, grow, work, live and age and the wide set of forces and systems shaping the conditions of daily life'* (World Health Organization 2021). They include education and employment opportunities, housing, social networks, location and how it facilitates other aspects of life such as diet, exercise and social connections (The Health Foundation 2019). It acknowledges that much more than 'medical' input is required for a healthy life. The Welsh Government (WG) set out a strategy in 2017, with one stated aim being to '*break the cycle'* of '*…the stubborn legacy of ill-health*' (Welsh Government 2017). It supports the approach of viewing healthcare as separate to medical care (Braveman & Gottlieb 2014), acknowledging the links between social prosperity and a healthier and happier population.

1.10.2 Prudent healthcare in Wales

In 2013, the Bevan Commission started the discussion on adopting a prudent healthcare approach to service delivery in NHS Wales (Aylward et al. 2013). Prudent healthcare aims to improve the health of the nation by following 4 principles (Figure 1.3) undefined

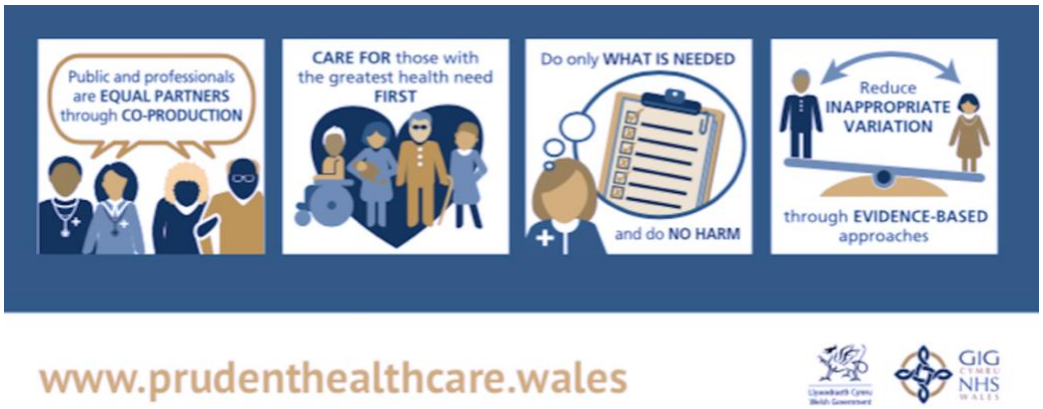


Figure 1.3: The four principles of prudent healthcare in Wales (Welsh Government and NHS Wales 2016)

Then Health Minister, Mark Drakeford set out the policy in January 2014 in a speech that included the line: "*I think that we have to move beyond the 'do no harm' principle to one which is focused on what is normally called minimum appropriate intervention. The principle that treatment should being with the basic proven tests and interventions…"* (Bradley et al. 2014). Chronic pain was one of the first four clinical services to be included in workshops used to test the principles. A 'Realistic Medicine' strategy was also launched in Scotland in 2016 (Calderwood 2017). Initiatives such as Quality Prescribing are based on the philosophy, as is most recently seen in guidelines for Chronic Pain (Harrison and Cormack 2018). Whilst there seems to be general agreement amongst healthcare professionals and organisations in Wales, that the prudent healthcare strategy is sensible, there remain barriers to its adoption (Addis et al. 2019). Outcome measures were reported by clinicians as a particular barrier to practising in an evidence-based way. Without understanding if what is currently being done is effective or not, it could be difficult to persuade people of the need for change (Addis et al. 2019). This is a pertinent consideration in relation to opioid medicines use, where there is a paucity of relevant data on clinically beneficial outcomes despite much evidence of their harms (Els et al. 2017).

1.10.3 Links between pain and deprivation

Pain is widespread in the UK population (Elliott et al. 2002; Fayaz et al. 2016). Prevalence estimates have ranged between 8 to 45% of the UK population living with some level of pain, since the early 1990s (Bowsher et al. 1991; Breivik et al.

2006; Fayaz et al. 2016). Whilst the condition is acknowledged to occur more frequently in areas of greater deprivation (Morgan et al. 2011; Todd et al. 2018; Gulliford 2020), the reasons for this are less well-defined. Pain is acknowledged to be a bio-psychosocial phenomenon (Eccleston 2011; Meints and Edwards 2018; Nicholas et al. 2019). How much of a role each constituent part plays in each individual's experience is very difficult to gauge. Engel (1959) suggested pain, whilst evolving from impulses received from the periphery for example, becomes separated from purely biological mechanisms and become phylogenetic and ontogenetically-led experiences (Engel 1959). Whilst perhaps some of the terminology used by Engel has left medical parlance, his theory has not. By 1977, Engel's theory had formed into the biopsychosocial model of pain that many pain management practitioners and researchers currently use as the basis for treatment (Engel 1977; Gatchel et al. 2007). That pain is a perception which can be affected by emotional inputs, good and bad, is not in doubt (Moseley & Vlaeyen 2015; Meints and Edwards 2018).

Of importance, when considering why some groups or individuals are more likely to experience long-lasting pain, is the impact of 'trauma' as being causative for some pain conditions. Conditions such as fibromyalgia and chronic fatigue, where there is not often a known cause of onset have been used as examples of trauma-linked pain (Scioli-Salter et al. 2015; Nicholas et al. 2019,). However, there appears to be an association between persistent stressors such as post-traumatic stress disorder and worsening pain experience (Abdallah & Geha 2017) for other conditions including back pain and knee pain (Asmundson and Katz 2009; Scioli-Salter et al. 2015; Meints and Edwards 2018).

There is similarity in neurobiology of stress or trauma responses and pain. Functional magnetic resonance imaging (MRI) has demonstrated specific areas of the brain respond similarly to stressful and painful stimuli (Tracey and Mantyh 2007; Tracey 2016). Pain and stress are considered to be adaptive responses. If unchecked, the response to either can become maladaptive, in other words,

more permanent physiological changes occur which place the individual into a more permanent state of suffering (Saariaho et al. 2011).

The link with socioeconomic deprivation is not entirely elucidated, albeit acknowledged that living a more impoverished life is a keen source of ongoing stress (Engel 1959; Loyland 2016). Children growing up in difficult circumstances are more likely to demonstrate adverse behaviours, linked to neurodevelopmental changes (McLaughlin et al. 2014; Mackes et al. 2020). Adverse life events as children, led to greater pain reporting in adulthood in the British Birth Cohort Study (1958) (Macfarlane et al. 2009). Simplistically, the association could be deemed a form of Pavlovian response (Moseley & Vlaeyen 2015, Abdallah & Geha 2017).

However, it is almost a certainly more complex picture as other life factors have also shown to be impactful on pain experience (Elliott et al. 2002; Macfarlane 2005; Moseley & Vlaeyen 2015). Indebtedness for example, has also been linked to chronic pain experience, with one study reporting a 30% increased likelihood of experiencing pain when indebted (Warth et al. 2019). Being in debt and experiencing deprivation were not directly linked, although pain experience was reportedly greater in the unemployed (Warth et al. 2019). Another theory which has been mooted is more mechanical in nature. Suggestions those living in more socioeconomically deprived areas are more likely to be employed in manual jobs (Crisp et al. 2009; Barnard 2018). Increased pain reporting has been observed in people, especially women who have physically active jobs (Rocha et al. 2017; Sorge and Strath 2018; Wu et al. 2020). This contrasts though, with evidence that being physically active is associated with reduced prevalence or longevity of painful conditions such as back pain (Smith et al. 2019).

1.11 Role of legislation and guidelines in controlling opioid analgesic prescribing

A major driver for changes to opioid management in the UK was the discovery and conviction of serial-killer Harold Shipman, who worked as a GP in Hyde, Manchester. In January 2000, Shipman was found guilty of killing 15 patients,

although he is estimated to have murdered at least 215 using high doses of opioid medicines (Baker 2004; Gallagher 2006). Following the Public Inquiries (Dyer 2004) into the circumstances surrounding his activities, several changes were made to legislation around controlled drugs such as morphine and fentanyl. The purpose of legislation changes was, in part, to make such behaviours harder to carry out but also easier to detect (Dyer 2004; Baker 2004; Gallagher 2006). The legislation changes came into effect during the 2005 – 2015 study period. Recently, the Gosport inquiry (2018) revealed the extent of deaths related to the over-prescribing and failure to act on concerns of such (Gosport Independent Panel 2018). Similarities with the Shipman murders are stark. Although not investigated and reported for 20 years, the first reports about the use of opioids in Gosport were made in 1991 and continued throughout the same time period that Shipman was active. A population of older, vulnerable patients were given opioid medicines under the guise of pain relief, predominantly by a single prescriber (Gosport Independent Panel 2018). Concerns were raised by other staff, on the basis that often, there was no indication for the analgesics and the patients targeted were not considered to be imminently dying or receiving palliative care (Gosport Independent Panel 2018; Knights et al. 2018; Pocock et al. 2018). What is not clear in this awful case, is whether the laws introduced following Shipman, would have led to a different outcome in Gosport. The concerns raised by staff were mostly clinical and about the appropriateness of the prescriptions. The post-Shipman legislation made no mention of clinical suitability, suggesting as long as prescriptions are written correctly, not issued in large quantities or at an unusual frequency, they might still slip under the radar (Dyer 2004; Department of Health 2013).

The introduction of National Prescribing Indicators was agreed in Wales in 2003, as a way of promoting rational prescribing (All Wales Medicines Strategy Group 2021). The first opioid analgesic prescribing indicator was created for the 2012/13 financial year and since then, been included every year (All Wales Medicines Strategy Group 2013). NICE clinical guidelines are intended for use in England and Wales and focus on condition management. Over the years, NICE

has progressed towards providing non-pharmacological as well as, pharmacological recommendations for treating and managing conditions. In relation to pain, NICE published guidelines for osteoarthritis (National Collaborating Centre for Chronic Conditions 2008), low back pain (National Institute for Health and Clinical Excellence 2008) and neuropathic pain (Centre for Clinical Practice at NICE 2013) between 2005 and 2015.

Since the early 2000's, significant increases in opioid prescribing have been observed in Wales (Davies et al. 2018) and across the UK (Zin et al. 2014; Jani et al. 2020). The trends noted in the UK, mirror what has been seen in other developed nations (Boudreau et al. 2009; Hamunen et al. 2012; Fischer et al. 2014; Levy et al. 2015; Wagemaakers et al. 2017). However, if pain prevalence is increasing or being maintained at a high level (Fayaz et al. 2016; Vos et al. 2017; Blyth and Schneider 2018), should it be a surprise to see increases in opioid analgesic prescribing?

Opioid analgesic prescribing is often discussed in terms of 'burden' and indeed, in Wales, prescribing indicators, developed to influence practise, refer to opioid burden (All Wales Medicines Strategy Group 2019). The implication of the term is of a 'heavy load' or at best, something that must be carried. In the case of opioids, who carries the burden? Is it the health service or the person taking the medicine?

1.11.1 Does anyone know how much opioid is too much?

More than 30 years ago, Portenoy (1986) discussed opioid safety in the context average doses of 40mg OMEQ per day (Portenoy and Foley 1986). Twenty years later, an average of 55mg OMEQ per day was reported (Korff et al. 2008). More recent studies however have shown a significant increase in the average dose of people reviewed, up to 140mg OMEQ in America (Dowell et al. 2016) and 86mg OMEQ in the UK (Zin et al. 2014). This, in spite of evidence that even when doses are significantly increased over a period of time, only a minority of people report meaningful improvement in pain and function (Trescot et al. 2008).

The opioid crisis in the USA gained first prominence in Washington State, where doses of opioids increased by 50% between 1996 and 2002 (Franklin et al. 2012). This led in 2007, to the development of state-wide, inter-agency guidelines on opioid dosing, including an opioid dose maximum of 120mg daily OMEQ. Within 5 years of the guideline's introduction, a 27% reduction in daily OMEQ of modified release opioids and 35% fewer people receiving more than 120mg OMEQ each day was reported (Franklin et al. 2012). Since then, recommended maximum OMEQ of 120mg per day have been incorporated into guidelines internationally, including here in the UK (All Wales Medicines Strategy Group and All Wales Therapeutics and Toxicology Centre 2020; Faculty of Pain Medicine 2021).

1.12 Why is research needed in Wales?

Pain is a major health and wellbeing concern worldwide (Blyth and Schneider 2018; Wu et al. 2020). It appears, from the last two Global Burden of Disease studies, the prevalence of long-term, disability related painful conditions are rising.(Hoy et al. 2014; Wu et al. 2020). An exploration of UK data from the 2016 Global Burden of Disease study revealed Wales to have higher rates of disability-adjusted life years for low back and neck pain (1,692 per 100,000 population) than either Scotland (1,654 per 100,000 population) or Northern Ireland (1,645 per 100,000 population) although rates in England were higher (1,820 per 100,000 population)(Steel et al. 2018). This is important, not least due to the significant burden pain places on healthcare systems and society more widely (Elliott et al. 2002; Hanna 2012, Takura et al. 2015). Furthermore, the economic implications of having a noteworthy proportion of any population living with pain and possibly unable to work as a consequence, are substantial (Phillips and Harper 2011; Gustavsson et al. 2012).

There are clear associations between pain and socioeconomic deprivation (Morgan et al. 2011), as there are with other long-term health conditions (Whynes 2008; Newton et al. 2015). Added to this, concerns about rising rates of opioid prescribing in the UK have escalated since the start of the 2000's (Zin et al.

2014; Ruscitto et al. 2015). This is in part, a result of the highly publicised problems experienced in North America (Weisberg and Stannard 2013; Vokinger 2018; Verhamme and Bohnen 2019) again, concentrated in areas of greatest socioeconomic deprivation (Kurani et al. 2020; Nowakowska et al. 2020). Wales is a country where a sizeable part of the population have poor health (Public Health Wales Observatory 2018; StatsWales 2020; NHS Wales 2021) and live in relative poverty (Barnard 2018). The number of people living with pain in Wales is unknown. An approximation of around 1.3million people affected, can be made based on prevalence estimations that up to 44% of the UK population live with pain (Fayaz et al. 2016).

It is known however, that analgesic prescribing has increased in Wales over the last 20 years (Welsh Analytical Prescribing Support Unit 2013; Statistics for Wales 2020). It is of particular concern not simply due to the risk of misuse (Amsterdam and Brink 2015; Morley et al. 2017) or disproportionate numbers of opioid-related deaths (Turner et al. 2019; Office for National Statistics 2021) but also long-term harms to general health and wellbeing (Els et al. 2017) in an already 'sick' population. Whilst research has been conducted on opioid prescribing in the UK (Zin et al. 2014; Ruscitto et al. 2015; Mordecai et al. 2018; Todd et al. 2018; Torrance et al. 2018), none has thus far been conducted in Wales.

Basic prescribing data, whilst useful for monitoring trends in the population as a whole (Shared Services Partnership 2021) do not allow detailed analysis (Curtis and Goldacre 2018) and this possibly limits the effectiveness of initiatives aimed at influencing it (All Wales Medicines Strategy Group 2019). Since 2012, there have been arbitrary targets to reduce opioid analgesic prescribing across Wales (All Wales Medicines Strategy Group 2013). What is difficult to determine is an acceptable level of prescribing, given the rising prevalence of conditions that may be deemed to be painful. If Wales has a higher-than-average burden of painful conditions in the population, would it necessarily be 'wrong' to have higher than average opioid prescribing?

1.13 Route into research

In 2013, Welsh Government's Advisory Panel on Substance Misuse asked for stakeholder evidence regarding misuse of prescribed analgesics. Whilst a final report was not published, a research briefing was released outlining the concerns about rising numbers of prescriptions, associated harms, misuse and deaths (Roberts 2016). The evidence gathered and research briefing, highlighted a general agreement amongst patients, practitioners and other stakeholders, that opioid prescribing was increasing and was creating problems for services and individuals. However, there were few detailed data on opioid prescribing, in particular examining who was receiving prescriptions or how prescribing differed across Wales. The challenge was laid down by the Chair of the Panel (Professor Phil Routledge) to find and analyse the data needed to provide some greater insight (Routledge 2013).

From those discussions and others with Welsh Government and organisations such as the All Wales Therapeutics and Toxicology Centre (AWTTC), issues of importance in relation to opioid prescribing were debated and developed into the following research questions:

- How has opioid analgesic prescribing changed over time?
- How do factors such as gender, age, or socioeconomic status effect the prescription of opioid analgesics?
- Have guidelines or legislation influenced opioid prescribing?
- Are there associations between receiving opioid analgesic prescriptions and use of healthcare services?
- Finally, and importantly for policy makers, how much does this cost the Welsh NHS?

Having this information might allow better targeted services and more prudent use of limited budgets. This thesis aims to make a start on answering those questions by using a large repository of Wales-specific healthcare data. The study will look back at the patterns of prescribing and healthcare use, and what might

have influenced them. It is hoped that by developing a better understanding of what has happened in the past, the future can be more effectively shaped.

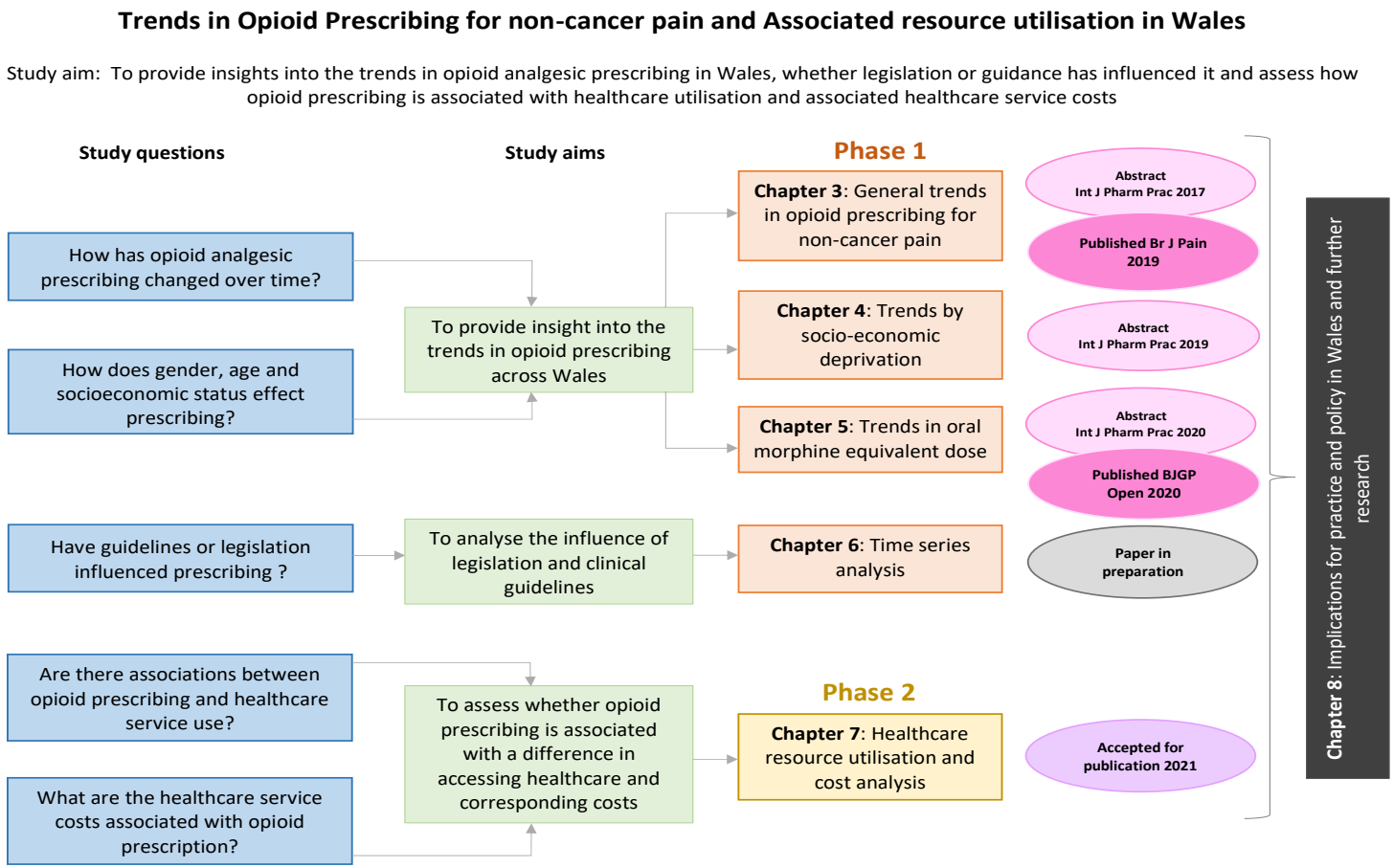
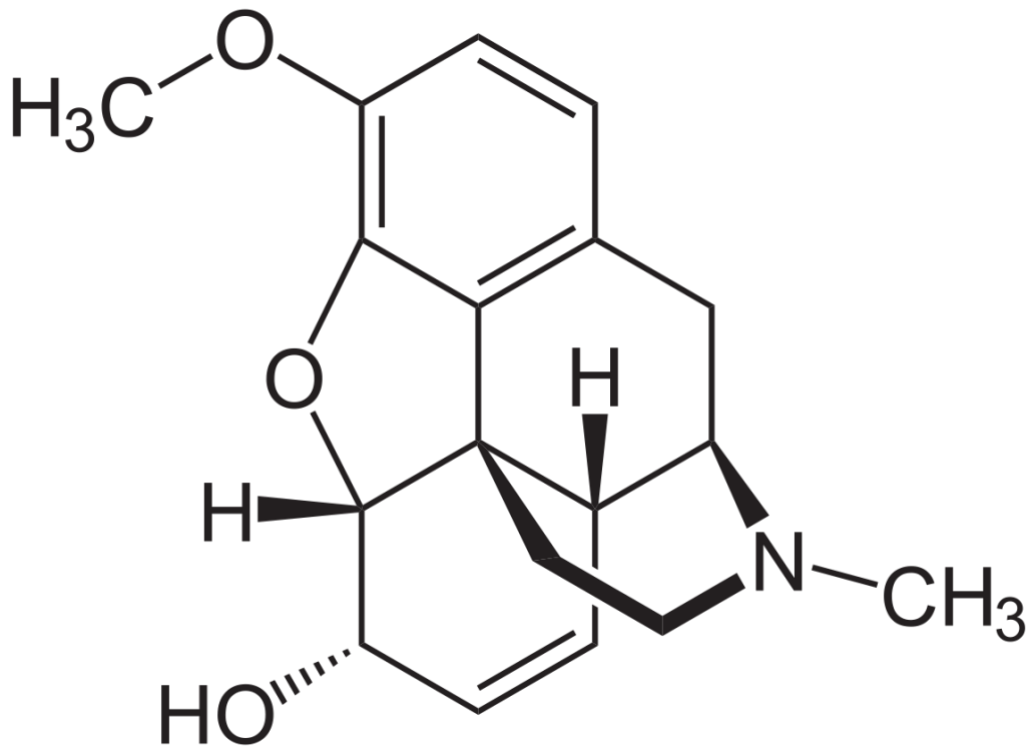


Figure 1.4: Overview of study including outputs generated up until July 2021

Chapter 2
Methods



"Though this be madness, yet there is a method in't."
William Shakespeare (Hamlet)

Chapter 2 - Methods

2.1 Chapter overview

In Chapter 1, how pain can be defined, and the social and economic burden of non-cancer pain were reviewed. How pain can be managed and where opioid analgesics fit into that was introduced, as were concerns about their potential harms. Aspects of socio-economic deprivation and how it affects healthcare outcomes across the UK and Wales in particular were presented. In this chapter, the research aims, and objectives are set out. The research strategy and overarching methodology is described, alongside statistical methods which are similar throughout the thesis. This chapter focusses on Phase 1 of the study, where prescribing trends were examined. Methods used in Phase 2, which analyses healthcare service use and associated costs, are found in Chapter 7.

2.1.1 What are the aims of this research?

There are three main aims to this research (Figure 1.4).

1. To provide greater insight of the trends in opioid analgesic prescribing across Wales, by examining individual demographic data for those people receiving prescriptions. This moves on from basic prescribing trends commonly used in practice. Gender, age and socioeconomic status are not routinely discussed or targeted by guidelines or prescribing initiatives (All Wales Medicines Strategy Group 2013; Welsh Analytical Prescribing Support Unit 2013; All Wales Therapeutics and Toxicology Centre 2021) but are likely to be important.
2. To analyse the influence of legislation and prescribing guidance on opioid prescribing. At the time of writing, Wales had not produced national guidelines for prescribing in pain management. Instead, guidelines from the National Institute for Health and Care Excellence (NICE) and National Prescribing Indicators (NPIs) are promoted to encourage rational, evidence-based prescribing. NPIs have included analgesic measures since 2009, (All Wales Medicines Strategy Group 2021) but, as with NICE, the

impact on practice is difficult to measure. Included, is a question of whether current methods of examining prescribing trends are accurate, in terms of opioid burden.

3. To assess whether opioid prescribing is associated with any difference in accessing healthcare. A cost-burden study for healthcare attendance will be undertaken to estimate the impact on NHS Wales. The intention is to share this information with Welsh Government, to inform debate on future goals of prescribing measures and how this all fits with the wider aims for a Healthier Wales (Welsh Government 2019).

2.2 Research objectives

To address the study aims, the objectives of this research were set out as follows

1. To examine prescribing trends of opioid analgesics between 2005 and 20015 and scrutinise whether trends differ between gender or different age-groups (Phase 1 - Chapter 3)
2. To determine if opioid analgesic prescribing trends are affected by socioeconomic deprivation status (Phase 1 - Chapter 4)
3. To analyse trends in oral morphine equivalent doses and prescribing duration using estimated measures for each (Phase 1 - Chapter 5)
4. To determine if general opioid prescribing trends appear affected by legislative or clinical guidance changes during the study period using time series analysis (Phase 1 - Chapter 6)
5. To assess the frequency of primary and secondary healthcare attendance by patients with defined non-cancer pain conditions receiving opioid analgesic therapy (Phase 2 - Chapter 7)
6. To estimate healthcare service costs associated with the use of opioid analgesics (Phase 2 - Chapter 7)

2.3 Research strategy

Opioid prescribing in Wales has not been previously examined. This study aimed to provide the starting point from which more research may build in future.

Qualitative enquiry around the reasons for prescribing, or attitudes of prescribers and people receiving prescriptions was not included in this research. A single hypothesis is not being tested here. Instead, there is an overarching study question, based on existing knowledge of opioid prescribing in the UK and associations with healthcare utilisation. Three research aims were developed and broken down into more specific analyses such as trends in opioid prescribing by age-group or gender.

Examining trends in prescribing, healthcare utilisation and associated costs is fundamentally a deductive process. A positivism paradigm would suggest that using quantitative methods to address the research questions posed would provide objective results (Kawulich 2012). Even with a study the size of the one described here, investigator bias could be introduced. For example, a clinical interest in opioid prescribing or professional experience of people coming to harm as a consequence of using them, might skew interpretation of the results. Consequently, it might be more accurate that the study epistemology is within a post-positivist framework, whereby perfect objectivity is aimed for but pragmatically, not achieved (Kawulich 2012; Khaldi 2017).

Both parts of this study required a form of census, with a range of population characteristics being measured (Lavrakas 2008) . Use of questionnaires or data from individual primary care practices or Health Boards was ruled out as viable methods for data collection due to the quantity of data needed to enable a Wales-wide picture. Surveying the population directly would also have required a significant amount of time and resource, with potentially limited return for the effort.

2.4 Study Design

The Trends in Opioid Prescribing for non-cancer pain and ASsociated healthcare utilisation in Wales (TOPAS) study was designed in two phases. The first set out to examine trends in opioid prescribing for non-cancer pain, across Wales between 1 January 2005 and 31 December 2015. Using a retrospective, repeated

cross-sectional design, similar to that used by other researchers in this area (Zin et al. 2014), trends in opioid prescribing and demographic influences were examined. Additionally, time series analysis was used to examine the effect of legislation and guidance on opioid prescribing. Phase 2 of the study was a retrospective, longitudinal case-controlled study. Frequency of healthcare service attendance by people with recorded diagnoses of conditions associated with pain, was assessed using linked data from primary and secondary care. Finally, each recorded interaction was attributed costs using nationally available unit cost data, in order to estimate healthcare service charges and determine associations with opioid analgesic prescribing.

2.4.1 The SAIL Databank

The SAIL databank was established in 2007, to ensure the copious amounts of routinely collected data from services in Wales was used to improve the quality of healthcare and other public services. Data are used to review service use, treatment outcomes and impact on the population of other public health initiatives such as respiratory health changes following housing improvements (Ford et al. 2009, Jones et al. 2019) . It is now housed in its own building, which enables physical security and access restrictions, in addition to the multi-layer technological safeguarding measures (Jones et al. 2019). As with the Clinical Practice Research Datalink (CPRD) (Wolf et al. 2019) and other data sources data are anonymised at source or by other third-party providers such as the Digital Health and Care Wales (DHCW) before it is accepted into the databank. By doing so, it is not possible for dataset reconstruction in an identifiable way (Ford et al. 2009; Lyons et al. 2009).

Data is gathered from primary care when practices opt to share the data they hold. Consequently, individual patients need to request their general practitioner does not share their data if they do not want them used (Secure Anonymised Information Linkage Databank 2021). Secondary care data such as inpatient admission and emergency department attendances are recorded automatically by data coders working in Health Boards across the country, and the data shared

nationally as part of the work of DHCW and Welsh Government. Whilst Wales has a relatively small population (3.15million in 2019), the SAIL databank provides data on 78% of it (2.5million) (Secure Anonymised Information Linkage Databank 2021). This makes the SAIL databank the most complete collection of health and social care data in the UK and reflective of the population it serves.

2.4.2 Anonymisation process and security

Ensuring the anonymisation and security of data for research purposes is crucial. Researchers should ensure their choice of data provider abides to high standards of security for data transfer and storage but also linkage, which are all measures of quality (Clinical Practice Research Datalink 2021; Doidge et al. 2020). The process of anonymisation used by the SAIL databank is similar to that used by other systems (Clinical Practice Research Datalink 2021). Probabilistic and deterministic linkage methods are used for linking datasets within the SAIL databank (Figure 2.1). When tested for accuracy, the SAIL databank was found to have rates of linkage accuracy greater than 90% and most, were greater than 99% (Lyons et al. 2009).

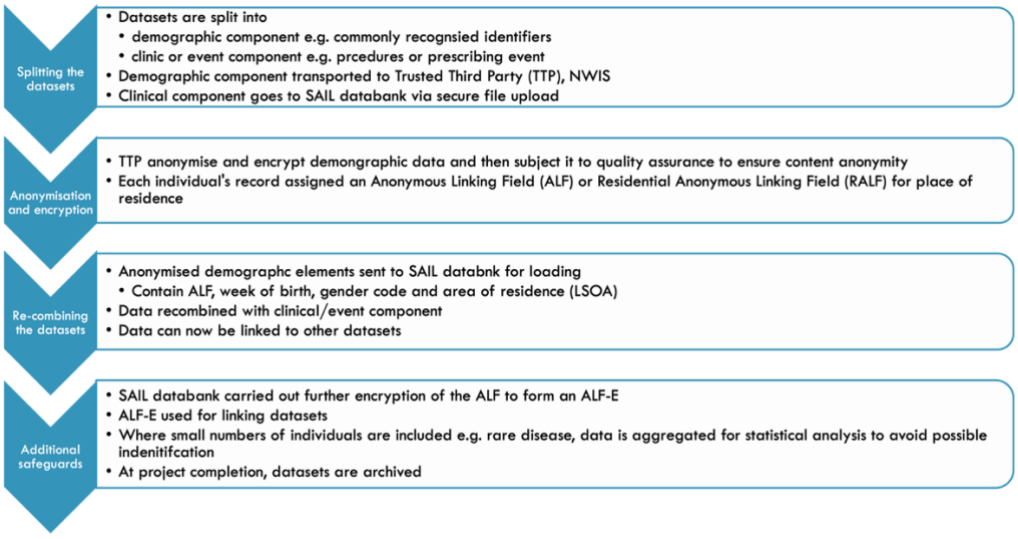


Figure 2.1: SAIL data anonymisation process (Secure Anonymised Information Linkage Databank 2021)

The security of data within the SAIL databank is closely monitored. All data extraction and analyses are undertaken via a secure server and accessed through an equally secure gateway (Jones et al. 2014). No data can be transferred in or

out of the gateway without being reviewed by data analysts from SAIL, who verify data falls within the agreed parameters and does not allow the possibility of unmasking individuals. Of keen interest are data with low frequency, which, SAIL is very cautious about allowing removal from the secure gateway, as in theory, they might be more easily identified (Ford et al. 2009; Jones et al. 2014).

2.4.3 Why the SAIL databank chosen for this study

Prescription numbers for opioids are routinely collected and used to track trends and mark against National Prescribing Indicators (National Statistics, Knowledge & Analytical Services 2015; All Wales Medicines Strategy Group 2019) (Chapter 6). Whilst data was and is available on prescription numbers and defined daily dose per 1,000 patients from Welsh Government sources, it is not possible to examine trends by anything more detailed than Practice level i.e., by the GP practice who supplies the prescription. Demographic exploration is also not possible with NHS prescribing data used by Health Boards and Government organisations in Wales (All Wales Therapeutics and Toxicology Centre 2021; Shared Services Partnership 2021). Whilst the socio-economic rank can be elucidated for the practice where a prescription originates, it will not necessarily correlate with the individual patient (Stats for Wales 2021). Prescribing data also does not permit examination of differences in gender or age. Without this knowledge, policy and guidance around prescribing may not reflect variance in practise and consequently, may be limited in effectiveness.

In order to understand the trends noted across Wales, being able to examine data to individual patient level is essential. The SAIL databank provides opportunity to trace individuals' interactions with the healthcare system as a whole, including conditions being managed and how they might fit with attendance and prescribing (Jones et al. 2014; Jones et al. 2019). The cost-analysis part of this research would not be possible without access to data, only available from the SAIL databank (Jones et al. 2019; Secure Anonymised Information Linkage Databank 2021). There are currently no other means of accessing individual's linked data from a single source, which, spans primary and

secondary care health services in Wales in addition to the demographic information necessary to make sense of it. Whilst other databanks such as Clinical Practice Research Datalink (CPRD) (Clinical Practice Research Datalink 2021) contain data from Wales, it is only a small part of the total data held and is focussed on primary care. Administrative Data Research UK (ADR UK) is another option for accessing Welsh data but uses the SAIL databank as its source for Wales in any case (Administrative Data Research UK 2021). A comparison of data sources within the UK, which were considered and rejected for use in this research is appended (Appendix A).

The research in this thesis required linked data from across Wales and coverage of all sectors of healthcare. The SAIL databank is the only available source of such complete data and is quality assured in terms of data collection, storage, linkage, analysis and release. Consequently, using the SAIL databank as the data source for this research, was the best option to determine the answers to the questions posed.

2.5 Ethical considerations

The SAIL databank provides anonymised person level routine data for research and evaluation (Ford et al. 2009; Jones et al. 2014). Data has commonly recognised means of identification removed before it is submitted to the SAIL Databank. It is considered impossible to reconstruct identities from within SAIL (Lyons et al. 2009). The Information Governance Review Panel (IGRP) of SAIL is an independent group of professionals from a range of organisations including Welsh Government, Public Health Wales and the local Health Board based in Swansea, as well as members of the public. Their role is to quality assure all applications for access to the databank (Ford et al. 2009) and they approved the TOPAS study in 2016 (Section 2.5.1). Consideration of the ethical implications of the study form part of the deliberations by the IGRP, prior to approval. Whilst people have the option of withdrawing their data from the SAIL databank, they must opt-out at the source of data entry e.g., their GP practice. It is therefore

incumbent on those inputting data at source, to ensure people are aware of the potential for it to be included in research studies.

2.5.1 Project Application, process and approvals

The project was discussed with a Senior data analyst from SAIL, as per the internal processes of SAIL (Secure Anonymised Information Linkage Databank 2021). The SAIL analyst wrote a scoping document, based on the discussions and study protocol, to detail the datasets the project would need to access (Appendix A). Following the scoping exercise, an estimate of the costs for the data analyst to undertake the extraction process, was provided by SAIL. Research funding applications were made and secured from Pharmacy Research UK (Ref. PRUK-2016-PA1-A), which allowed progression of the project. Approval for the data extraction was subsequently sought and obtained from the IGRP by submission of the project protocol (Appendix A) and application (scope) form (Appendix A). After consent for the research was gained, Safe Researcher Training was undertaken, and evidence of qualification submitted to SAIL, as part of the quality assurance processes for the organisation. On completion of these processes, access to the secure online gateway where the extracted datasets could be gained, was permitted and the project was able to start. Following study approval; a detailed specification for data extraction was developed with the Prudent Healthcare Intelligence Hub (PHIH) team from the Farr Institute, Swansea University (Appendix A). To enable effective dataset identification, a range of inclusions and exclusions were developed based upon the study protocol (Appendix A).

2.5.2 Data sources

A split file approach is used to import person level datasets into the secure environment of the SAIL databank. The method facilitates linkage whilst maintaining the anonymisation and confidentiality of the records (Ford et al. 2009; Lyons et al. 2009). Several datasets were used to build the TOPAS data tables:

- Welsh Demographic Service Dataset (WDSD) includes demographic information such as week of birth, Low Super Output Area (LSOA), Residential Anonymised Linking Field (RALF) (in lieu of addresses), Welsh Index of Multiple Deprivation (WMID) scores, Health Board of residence for each residency period using Local super Output Area (LSOA) levels and registration to General Practitioners in Wales.
- Welsh Longitudinal General Practice (WLGP) data (GP event data) is a record of all interactions in primary care. It is formed by extracting data from 78% of Welsh General Practice. Data are recorded using specific event codes in Read-code format and an encrypted Anonymised Linkage Field (ALF) for each patient. The ALF can be used to link that individual's records to all other datasets available within the SAIL databank, where they have data recorded.
- Annual District Death Extract (ADDE), which the Office for National Statistics (ONS) provides SAIL with date of death, primary and secondary causes of death via the national repository of mortality data.

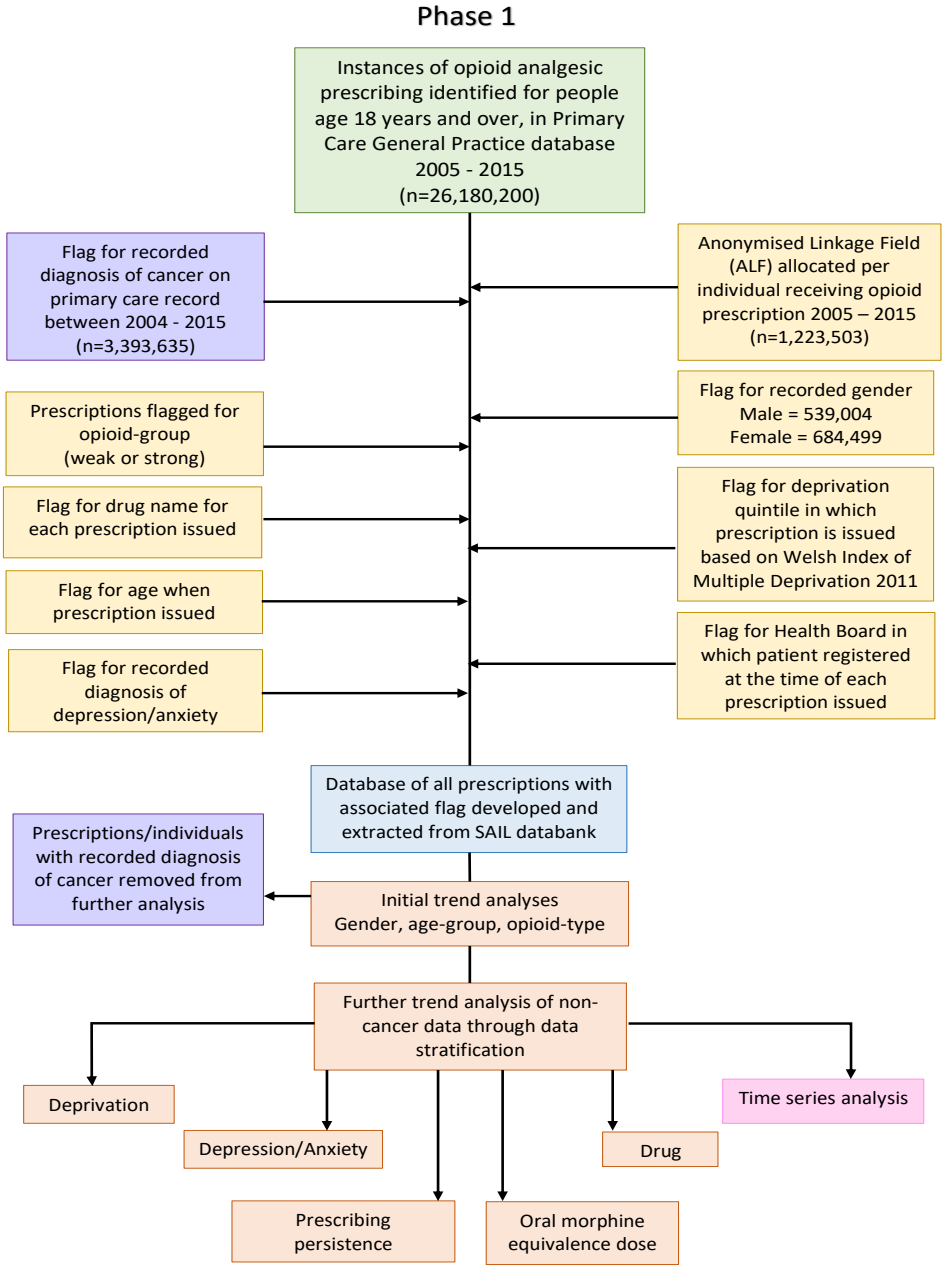


Figure 2.2: Diagrammatic view of data extraction and organisation for phase 1 trend analysis of opioid prescribing 2005 – 2015

The methods used throughout the research are described below where they are common to more than one chapter. Methods used to undertake specific data preparation, extraction or analyses are set out in more detail in the corresponding chapters.

2.6 Data compilation

Due to issues of data security, a Research Data Analyst from the Prudent Healthcare Intelligence Hub (PHIH), a section of the Centre for Improvement in Population Health through E-records Research (CIPHER) within the Farr Institute and based at Swansea University, undertook the compilation of data tables from the SAIL Databank. The compiled read-code lists, and other data specifications were used to assemble a series of data tables, which were then linked (Section **Error! Reference source not found.**). A master table was devised, which included separate columns, known as 'flags' for certain criteria such as 'weak' or 'strong' opioid in order to scrutinise the datasets.

2.6.1 Identifying Phase 1 study subjects

A list of opioid medicines was based upon a file shared by colleagues at University of Nottingham (Appendix A), who examined trends in strong opioid prescribing using CPRD, which provides predominantly English data (Zin et al. 2014). The Nottingham list was expanded on the basis of Welsh prescribing data taken from NHS Wales using the Comparative Analysis System for Prescribing Audit (CASPA) (Shared Services Partnership 2021), which demonstrated the range of opioid medications in use over the study period (2005 to 2015) (Appendix A). Sixteen drug categories (buprenorphine, codeine, dextropropoxyphene, diamorphine, dihydrocodeine, dipipanone, fentanyl, hydromorphone, meptazinol, methadone, morphine, oxycodone, pentazocine, pethidine, tapentadol and tramadol) were included. Read-codes, a thesaurus of clinical terms, used to record all interactions, diagnoses and interventions throughout Primary Care in the NHS, until 2018, were used to develop a list of all products to be included. Lists of read-codes were compiled from the Clinical Terminology Browser available from the NHS Information Authority and accessed via the SAIL gateway. All analgesic products containing the 16 drugs, including where an opioid was combined with another medicine e.g., co-codamol (codeine and paracetamol), were included and identified by their individual read-code.

The list was checked against both versions of read-codes available (v2 and v3) to ensure maximum data extraction.

The WLGP database was searched, and every opioid prescription noted within the study period, 1 January 2005 to 31 December 2015 was identified. Corresponding event dates, ALF, demographic information (gender, LSOA, WIMD) were collected using the anonymised linkage systems in place within SAIL (Section 2.4.2). The data was subjected to repeated cross-sectional sampling to determine monthly and annual time-series, prescribing trends over the study period.

2.6.2 Exclusion of individuals with cancer diagnoses

This research was concerned with non-cancer related opioid analgesic prescribing. Therefore, following the identification of all relevant opioid prescriptions, data were stratified into cancer and non-cancer groups. A validated list of cancer read-codes was shared from University of Nottingham (Appendix A), checked and verified by the author to ensure both available versions of read-codes (v2 and v3) were included. The cancer group included any individual with a cancer diagnosis in their Primary Care General Practice medical record at any time during the study period (2005 – 2015) or with a qualifying cancer event recorded in the 12 months prior to the study period i.e., between 1 January and 31 December 2004. Data pertaining to individuals with cancer diagnoses were removed from the main dataset and so excluded from the study analyses presented in this thesis.

2.6.3 Drug classification

Within the data tables extracted from the main SAIL datasets, the exact product details and a grouping opioid name e.g., codeine were included to assist with categorisation. All opioid analgesics included were categorised into weak or strong (Table 2.1) based on recognized listing by the World Health Organisation (World Health Organisation 2019) and the British National Formulary (BNF: British National Formulary - NICE. 2021) and clinical guidelines, where drugs

might be categorised on the basis of the order they get used in practice (Scottish Intercollegiate Guideline Network SIGN 2019).

Table 2.1: Study categorisation of weak and strong opioids

Weak opioid	Strong opioid
Buprenorphine 5, 10, 15, 20 micrograms/hour patch	Buprenorphine – S/L preparations <2mg, ≥35micrograms/hour patches
Codeine	Diamorphine
Dihydrocodeine	Fentanyl
Dextropropoxyphene	Hydromorphone
Dipipanone	Methadone – tablets only
Meptazinol	Morphine
Pentazocine (with paracetamol)	Oxycodone
Tramadol	Pentazocine
	Pethidine
	Tapentadol

2.6.4 Age and age-group formation

Age was calculated based on the week of birth (Monday preceding birth as per SAIL protocol) (SAILdatabank.com). Initially, the range of ages of people included in the study was calculated by assigning their age at an index date of 1st January 2016. For those people who died during the study period; age at the date of death was reported. However, use of the index-date led to data being skewed, particularly in terms of people in the younger age-groups. Consequently, age at the time the prescription was issued, was used. Welsh Government use a 16 to 24 years age-group (StatsWales 2021 and this was adjusted to 18-24 years to bring the study in line with others from the UK where 18 years old was the youngest age included (Torrance et al. 2014; Zin et al. 2014). Data relating to patients aged less than 18 years were removed and only patients aged 18 years or over at any time during the study period (2005 – 2015) were selected for further analysis. Extracted data were sorted into the designated age-groups chosen for this study, 18-24 years, 25-44 years, 45-64 years, 65-74 years, 75-84 years and 85+ years groups, mirroring the groupings used by Welsh Government. Data were stratified by age-group for comparison of prescribing trends.

2.6.4.1 Age-group population calculations

Annual population estimates by age, are available from StatsWales (StatsWales 2021). Data for each year, 2005 to 2015, for each age from 18 years to the maximum recorded, were extracted in an Excel file. The percentage of the total Welsh population each age-group comprised, was calculated for each year. The percentages were then used to determine the SAIL population for each age-group, using the previously calculated SAIL annual populations. The annual SAIL populations per age-group were used to adjust the number of people and prescriptions issued to each people within each age-group to per 1,000 age-group adjusted figures (Appendix A), providing a more balanced comparison.

2.6.5 Standardising population estimates

At the time of this study, the SAIL databank contained data for 78% of the Welsh population Databank 2021). As data become available to SAIL, it is backdated in the databank, so there was consistent representation throughout the study period. However, representation of each Health Board within the SAIL databank is proportionally different (Table 2.2). To determine population adjusted data, a method for populace estimation was devised.

Table 2.2: Representation of General Practice within SAIL Databank by Health Board

	2015 Population (% total)	**Number of GP Practices (% Wales total)**	**GP Practices registered with SAIL (% SAIL total)**
Wales total	3,099,086 (100)	443 (100)	345 (78)
Health Board (HB)			
Abertawe Bro Morgannwg	525,466 (17)	73 (16)	70 (20)
Aneurin Bevan	581,789 (19)	82 (19)	57 (17)
Betsi Cadwaladr	694,473 (22)	109 (25)	82 (24)
Cardiff and Vale	484,752 (16)	66 (15)	53 (15)
Cwm Taf	296,735 (10)	43 (10)	33 (10)
Hywel Dda	383,229 (12)	53 (12)	43 (12)
Powys	132,642 (4)	17 (4)	7 (2)

The Health Board areas used for the TOPAS study came into force in 2009 when new organisations were formed (NHS Wales 2009). Mid-year populations estimates for each Health Board (Table 2.2) were taken from StatsWales (StatsWales 2021) for the years 2009 – 2015. The proportion of the total Welsh

population living within each Health Board area was calculated. The percentages were used to calculate equivalent Health Board populations between 2005 and 2008 prior to the new organisations' emergence. The calculated or extracted population of each Health Board was adjusted to reflect their percentage representation in the SAIL databank. Population totals for each health board were added together to give an annual total for the SAIL databank. Calculated population numbers were divided by 1000 in order to calculate results per 1,000 population (Figure 2.3).

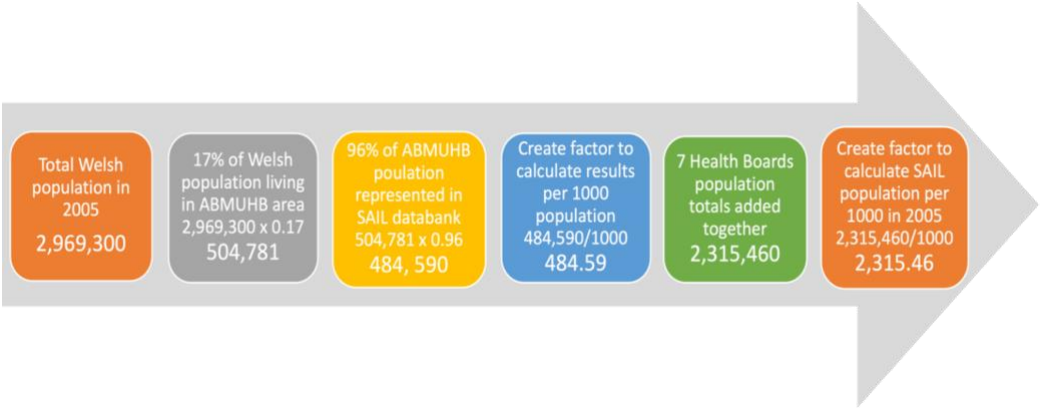


Figure 2.3: Method for calculating SAIL databank population for the TOPAS study, using Abertawe Tawe Bro Morgannwg University Health Board (ABMUHB) population 2005 as an example factor

2.6.5.1 Gender population standardisation

Yearly estimates of Welsh population by gender are available from StatsWales (StatsWales 2021). The population estimates for 2015 given by gender and by Health Board, for people aged 18 years and over, were extracted into an Excel spreadsheet (Appendix A). Percentage representation of women and men were calculated for each Health Board (Figure 2.4). The percentages were used to compute the population of men and women each year of the study and further adjusted to provide population per 1,000 that were subsequently used to amend the numbers of people and prescriptions throughout the study.

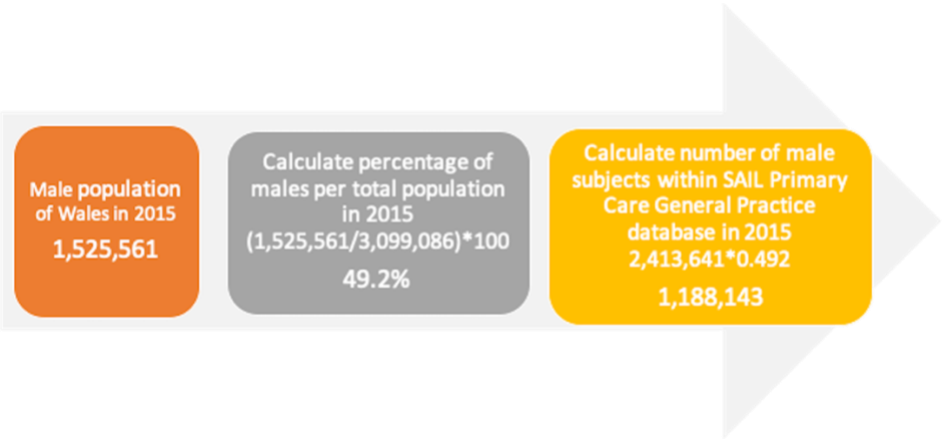


Figure 2.4: Calculating gender-adjusted population using male population in 2015 as an example factor

2.6.5.2 Population standardisation for deprivation quintiles

To enable population-standardised data for the deprivation studies, local super output area data (LSOA) was used to calculate the annual population assigned to each deprivation quintile per Health Board area. LSOAs are small areas accounting for around 1500 people, which are assigned a deprivation score. Those scores are then ranked and further assigned into quintiles where 1 is the most deprived and 5 the least. These are then used to develop the Welsh Index of Multiple Deprivation (WIMD).

The percentage of each Health Board population living in each WIMD2011 (the WIMD for 2011 chosen for use in this study) quintile was calculated and used to adjust to the general practice primary care population represented in SAIL (Appendix A). Estimated populations for each quintile were totalled to provide national numbers and used to adjust results and provide 'per 1,000 quintile population' results. A more detailed description of LSOAs, WIMD and the population calculations is included in Chapter 4.

2.6.6 Condition-linked data

Initially, it was hoped data extraction would allow an estimation of prevalence of pain-associated conditions and/or depression and anxiety within the whole population and compared to those receiving opioid analgesic prescriptions (Section 1.7). Consequently, read-code lists were developed (Appendix F and Appendix H) to identify individuals who had at least one of six pain-related

conditions: rheumatoid and osteo-arthritis, back and neck pain, neuropathic pain and fibromyalgia, or codes related to depression and/or anxiety on their primary care records. For Phase 1 of the study, the pain-associated condition data was not used to examine the whole SAIL dataset. Instead, data was linked only to those also receiving opioid analgesic prescriptions, which did not therefore provide an accurate reflection of prevalence. Consequently, the condition data was used only to identify subjects for Phase 2 of the study (Section 7.4.2).

A request was made to SAIL for a table to contain data for all individuals aged 18 and over, with data in the SAIL databank who had a record of depression and/or anxiety on their Primary Care record. The table was cross-referenced with the main TOPAS data table (individuals receiving opioid analgesic prescriptions) and details of any individual whose data appeared in both tables was to be extracted into a third dataset. The new dataset was to contain data for any person, aged 18 or over, with a recorded diagnosis of depression and/or anxiety and who received a prescription for at least one opioid medicine between 2005 and 2015. Within the main TOPAS dataset, a flag was added to indicate individuals with a recorded diagnosis of depression and/or anxiety. Following analysis of the data, clarification of the method of subject identification was requested from SAIL, but not provided. The data could not, therefore, be validated for the main thesis but does show some interesting signals and so is included in Appendix H and should be subject to further research.

2.6.7 Data extraction and analysis

In order to extract data for descriptive analysis, Structured Query Language (SQL) coding based on the study meta-data (Table X) was used, to interrogate the main data tables.

SQL is standardised programming language used for managing relational databases and performing operations on the data in them. Developed in the 1970's, SQL is used by data analysts for setting up and running analytical queries (Techtarget 2021).

Table 2.3: Principal metadata for prescription trend analysis (TOPAS_20170419)

Column name	Description	Project specific detail
EVENT_DT	Date of event	Date of prescription
ALF_PE	Unique patient identifier	
GNDR_CD	Gender code	1=Male 2=Female
DRUG_CAT	Drug name	Tramadol, Morphine etc
W_S	Weak / Strong categorization	
CANCER	Cancer patient flag	Cancer = 1 (if patient had cancer diagnosis in study period 2005-2015)
LHB_DESC	Local Health Board Description	7A1 – Betsi Cadwaladr 7A2 – Hywel Dda 7A3 – Abertawe Bro Morgannwg 7A4 – Cardiff and Vale 7A5 – Cwm Taff 7A6 – Aneurin Bevan 7A7 – Powys
WIMD2011_5TH	5 Decile	Welsh Index of multiple deprivation
DRUG_USAGE_PERIOD	Flag for short term / long term use	1 = short term user (<182.5 days) 2 = long term user (>182.5 days) 3 = other (includes non-actives)

SQL coding was written and entered into the SQL Editor of Eclipse SDK software (Figure 2.5). Each search was run, and the results extracted from Eclipse SDK into Excel 2016 spreadsheets and subsequently to IBM SPSS Statistics v26 software for further analysis. Extracted data was presented as frequency tables and then rearranged for analysis by SPSS (IBM Corporation 2021).

NUMBER OF PRESCRIPTIONS PER YEAR PER CANCER PER W_S PER DRUG USE PERIOD

SQL coding	Explanation
select	Selecting data for
distinct w_s,	weak or strong opioids
year(event_dt)ev_yr,	data for each year (2005 – 2015)
count(*)pres_cnt,	number of prescriptions
count(distinct alf_pe)pt_cnt,	number of individual patients
cancer,	cancer diagnosis or not
drug_usage_period	banding of time period of active
prescription	
from	

SAILW0507V.TOPAS_20170419	main data table for the TOPAS project
group by	results table to have the following columns
w_s,	weak or strong opioid
year(event_dt),	year
cancer,	cancer diagnosis or not
drug_usage_period	banding of time period of active prescription
order by	data to be presented by
ev_yr	year (2005 – 2015)

Figure 2.5: Example and explanation of SQL code for data extraction

In order to perform statistical analysis, the main data table from SAIL was downloaded into SPSS. The table was cleaned to remove unnecessary columnar data. For example, there were multiple gender codes taken from the Primary Care General Practice database; there were 8 possible causes of death available although it was rare that more than 2 were completed. Replicated or unneeded data were removed and then split into cancer and non-cancer tables. The non-cancer table was further split into weak and strong opioid tables to improve the processing speed.

2.6.8 Data security and quality assurance

All data processing was performed within the secure SAIL gateway and stored on SAIL servers. The in-house quality assurance processes were applied to each data extraction undertaken by the SAIL analyst as the study tables were compiled (Jones et al. 2019). When data processing was complete, a request to extract results tables and graphs was made to SAIL. The SAIL Data Guardian who ensures any risk of disclosure has been assuaged, assesses all requests for data extraction. If the requests met the criteria for release, it was then downloaded from the secure gateway and could be used to develop tables and figures for inclusion in the thesis (Secure Anonymised Information Linkage Databank 2021).

2.7 Statistical analysis

The study produced a large amount of data and a range of variables which lent themselves to a number of different analyses. The study population for the

Phase 1 study, were selected from the whole of the SAIL databank based on the presence of opioid prescriptions on the primary care medical record, therefore, normal distribution was not assumed. Shapiro-Wilks confirmed Phase 1 data were not normally distributed and so non-parametric tests were selected for the analysis (Chapter 3, Chapter 4 and Chapter 5). The trend analysis for phase 1 concentrated initially on examining the distribution of e.g., prescriptions over the 11-year study period and examined correlation between time and prescribing rate over that time. In addition to trend analysis, differences between groups e.g., ordinal variables such as socioeconomic quintiles and binary variables e.g., gender, weak or strong opioid groups, were used to stratify datasets before comparisons were made between the trends in each group. The rate of change was also used as the basis for investigating the effect of legislation or guidelines

Phase 2 of this study selected a cohort of individuals again from the whole SAIL databank population which represents 78% of the Welsh population. The study cohort was determined by diagnosis (Section **Error! Reference source not found.**) and then further stratified by opioid prescription. It might be assumed that due to the census-type data selection, normal distribution would not be likely. However, due to the large sample size in both arms of the study (case and control), we determined parametric tests could provide accurate analysis. As with Phase 1, descriptive statistics were used to examine patterns of healthcare use and associated costs in case and control groups and comparisons between and within groups, using categorical variables, to stratify groups. Regression analyses were also undertaken to examine the relationships between variables and the study outcome of healthcare utilisation. Whilst parametric testing was used for analysis, to ensure it was an accurate representation of the data, non-parametric tests were also performed. The output of those analyses is presented in Appendix F.

2.7.1 Spearman's rank correlation

Spearman's rank correlation (Spearman's Rho) is a non-parametric measure. It assesses how the relationship between two variables is described or the

statistical dependence between them. For this study, Spearman's rank correlations were used to determine the relationship between time and the rate of prescribing (Chapter 3, Chapter 4 and Chapter 5). This method of examining change over time was described by Mordecai et al in 2018 (Mordecai et al. 2018). The closer to 1.000 or -1.000 the result of Spearman's rank correlation is, the stronger the relationship between the two variables e.g., Spearman's r>.999 indicates the rate of prescribing was strongly linked to time or, more simply, prescribing increased over time.

2.7.2 Mann-Whitney U tests

The Mann-Whitney U test is a non-parametric test that examines differences between two groups or populations. It takes the null hypothesis to be that for randomly selected values (A and B) from two groups, the probability of A being greater than B is equal to the probability of B being greater than A.

Mann-Whitney U tests were used to examine differences between e.g. the number of strong opioid prescriptions per 1,000 population received by men or women (Chapter 3, Chapter 4 and Appendix B). For the purposes of this study, the tests examine all 11 years of data, rather than differences in the trends described.

2.7.3 Kruskal-Wallis tests

The Kruskal-Wallis test is an extension of the Mann-Whitney U test. Again, it is a non-parametric test used to compare two or more groups. Whilst Kruskal-Wallis can determine if a difference exists e.g., if one group is dominant or greater for example, it does not pinpoint where exactly that difference lies. Consequently, pairs of data are also contrasted using Dunn's pairwise comparison and Bonferroni correction. These tests are used in this study to compare e.g., how the number of prescriptions issued between 2005 and 2015 differ between quintiles of deprivation (Chapter 4 and Appendix C). Kruskal-Wallis tests might suggest more prescriptions are issued in some quintiles than others but do not reveal where the differences lie. Dunn's pairwise comparisons provide that

detail. For example, following a statistically significant Kruskal-Wallis test, Dunn's pairwise comparison might then illustrate more prescriptions are issued in quintile 1 compared to quintile 2, but more prescriptions are issued in quintile 2 than in quintile 3.

2.7.4 Time series analysis

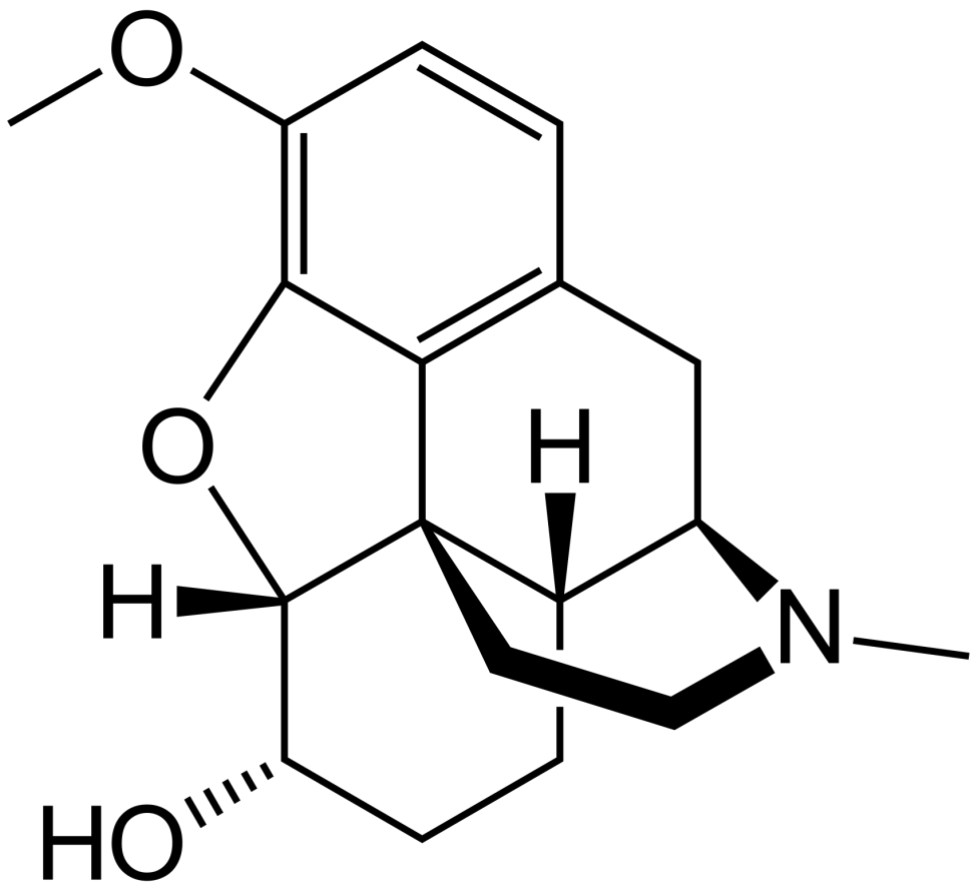
Interrupted and continuous times series analyses were conducted to examine whether changes in UK legislation or Welsh National Prescribing Indicators impacted prescribing trends between 2005 and 2015. An explanation of the methods used is provided in Chapter 6.

Continuous TSA was conducted using SPSS v26 software (IBM Corporation 2021) to sort the data and Microsoft Excel software (Microsoft Corporation 2018) to undertake calculations and plot graphs. Interrupted TSA analyses were completed using SAS 9.4 software (SAS Institute Inc 2021).

Phase 1

Chapter 3

General trends in opioid prescribing for non-cancer pain



"If you do what you've always done, you'll get what you've always got."
Henry Ford

Chapter 3 – General trends in opioid prescribing for non-cancer pain

3.1 Chapter overview

In Chapter 1, the background information which formed the overarching aims for this research were introduced and discussed. In Chapter 2, the methods adopted for the project were set out. In this first chapter of Phase 1, the main trends in opioid analgesic prescribing in Wales, between 2005 and 2015 will be presented. In addition to analysing the overall trends in terms of number of prescriptions, the data will be stratified by opioid-type (weak or strong opioid), gender and age. An overview of prescribing persistence throughout the study period is also examined.

3.2 Study objective to be addressed in this chapter

- To examine prescribing trends of opioid analgesics between 2005 and 20015 and scrutinise whether trends differed between gender or different age-groups

3.3 Background

Before this study was conceived, the number of prescriptions for opioid analgesics being issued in Wales, was known to have increased (All Wales Medicines Strategy Group 2013). Studies from across the UK had been published, raising opioid prescribing as a concern. Zin et al. (2014) published one of the first UK studies, examining the changes to strong opioid prescribing and stratified by diagnosis (cancer or non-cancer), defined daily dose and oral morphine equivalent and days of supply (Zin et al. 2014). Ruscitto et al. (2015) examined prescribing trends of opioids and other analgesics over a 16-year period in Tayside, Scotland. Results were presented by numbers of prescriptions and stratified by drug, individuals age and gender (Ruscitto et al. 2015). Bedson et al. (2016) looked at changes in the incidence of long-term opioid prescribing in a UK primary care population, from 2002 until 2013. Trends were broken down by gender and age-group, as well as the release-profile of the opioid analgesic.

Taking the example from previous authors, the results presented in this chapter will examine the numbers of opioid analgesic prescriptions issued each year between 2005 and 2015 and adjusted to population. Gender (Section 1.8) and age (Section 1.9) have been demonstrated to be factors which can impact pain prevalence and potentially therefore, prescribing. Consequently, data are examined in those stratifications. Opioid analgesics are divided into 'weak' or 'strong' classifications (Section 2.6.3) and so trends within those groups are analysed. Finally, as Bedson et al. (2016) demonstrated, long-term prescribing is known to have increased in the UK (Bedson et al. 2016) but has not been specifically examined in Wales previously. An estimated measure of opioid prescribing persistence was developed for this study and preliminary results presented here.

3.4 Method

3.4.1 Trend analysis

Individuals were identified and corresponding data relating to opioid prescriptions and demographics, extracted from the SAIL databank as described in Section 2.6. The number of prescriptions issued each year were totalled and also adjusted to population, with descriptive statistics used to describe the trends observed. Spearman's rank correlations (Section 2.7.1) were used to examine the change in prescribing rate over the study period, using all data between 2005 and 2015, in addition to calculating percentage changes over time.

Data were stratified into groups based on gender (Section 2.6.5.1), age-group (Section 2.6.4) and also the type of opioid prescribed on each individual prescription (Section 2.6.3). Comparisons of the number of prescriptions or prescribing rate, between genders and drug-type were made using Mann-Whitney U tests (Section2.7.2). Comparisons between age-groups used Kruskal-Wallis tests, with Dunn's pairwise comparison and Bonferroni corrections to confirm where any statistically significant differences were (Section 2.7.3).

3.4.2 Determining prescription persistence

Controlled drug prescriptions (which include opioids), have a legally valid duration of 28 days, after which time the prescription cannot be dispensed. Practice guidelines advise prescribers not to prescribe greater than 30 days of controlled drugs on a single prescription (Royal Pharmaceutical Society of Great Britain 2021)

At the time of data extraction, the SAIL databank did not include dispensing data, which would allow analysis of dosing instructions provided with the prescription and quantity of medicine prescribed. From that data, it would be possible to determine the daily dose of each medicine prescribed and make an estimation of the duration of use for the prescription issued. Consequently, prescription persistence was estimated by tracking the days between prescriptions issued, for each individual in the dataset. The total number of days between the first prescription issued and the final one, where each prescription was issued within 31.5 days of the previous one, was listed as the total prescribing period. Where a second prescription was not issued within 31.5 days of the first, it was listed as a one-off prescription.

3.4.2.1 Trends analysis

Data was stratified by year, to develop trend analysis of prescribing persistence between 2005 and 2015. All prescriptions issued to any individual were examined. The year in which the prescribing period ended was used as the index date for each prescribing period. For example, an individual receiving 3640 days of prescription coverage, starting in 2005 and ending in 2014, would be counted in the 2014 total, despite having data in every year between.

3.4.2.2 Stratification of prescribing persistence data

For the purposes of this analysis, data were examined for an individual's opioid use over a period of time, rather than examining by each individual drug prescribed. Data were stratified by the type of opioid prescribed at the end of each prescribing period. For example, where a person had a period of prescribing

which ended with morphine, a 'strong' opioid, they would be flagged as 'strong opioid' even if earlier in the prescribing period, they had been prescribed a 'weak' opioid. Data were also stratified by gender and socioeconomic deprivation quintile as previously described and adjusted to population (Appendix G).

3.5 Results

Between 2005 and 2015, 22,786,565 opioid analgesic prescriptions were issued to 1,099,026 individuals with non-cancer diagnoses whose data was contained in the SAIL Databank. Trends in the number of people receiving prescriptions were analysed and followed similar patterns to those of the numbers of prescriptions. Consequently, those results are not presented in this chapter but are included in Appendices B, C and D.

3.5.1 Overview of prescribing trends

Total opioid prescribing rate increased by 49.7% between 2005 and 2015 (Table 3.1). Between 2005 and 2010, the annual number of opioid prescriptions issued increased 27.5% (from 696.8 to 888.2 prescriptions per 1,000 population). There was a slower increase of 12.7% (from 888.2 to 1000.7 prescriptions per 1,000 population), between 2010 and 2015 (Appendix B). However, while the increasing trend in the number of people being prescribed opioids had started to decline, the number of prescriptions issued each year was still increasing at the end of the study period (**Error! Reference source not found.**).

Table 3.1: Changes in number of prescriptions issued between 2005 and 2015

Group	2005	2015	Change in variable	Percentage change (%)	Spearman's r, p-value
Total					
Prescriptions	1,613,417	2,415,374	801,957	49.7	>.999, p<.001*
Prescriptions per 1,000	696.8	1000.7	303.9	43.6	>.999, p<.001*
Weak opioids					
Prescriptions	1,520,441	2,021,677	801,957	33.0	0.945, p<0.05*
Prescriptions per 1,000	656.6	837.6	181.0	27.6	0.909, p<0.01*
Strong opioids					
Prescriptions	92,976	393,697	300,721	323.4	>.999, p<.001*
Prescriptions per 1,000	40.2	163.1	123.0	306.2	>.999, p<.001*

*p<0.05 = statistically significant. Annual data Appendix B

3.5.2 Trends in prescribing by type of opioid analgesic

Between 2005 and 2015, weak opioid prescribing rates rose by 27.6%, with a strong correlation confirmed by Spearman's Rho (Table 3.1). Weak opioids prescribing peaked in 2012 following a 30% increase (from 656.6 to 853.8 prescriptions per 1,000 population) (Figure 3.1). Whilst overall annual numbers of prescriptions rose over the 11 years of the study, there was a 1.9% reduction (from 853.8 to 837.6 prescriptions per 1,000 population) in prescription rate between 2012 and 2015 (Figure 3.1 and Appendix B).

Strong opioid prescribing rates increased by 306.2% (from 40.2 to 163.1 prescriptions per 1,000 population) over the study period (Table 3.1). In the first 6 years of the study (2005 to 2010), prescribing increased 112.4% (from 40.2 to 85.3 prescriptions per 1,000 population). From 2010 until the end of 2015 however, the overall change was 91.2% (from 85.3 to 163.1 prescriptions per 1,000 population) (Figure 3.1).

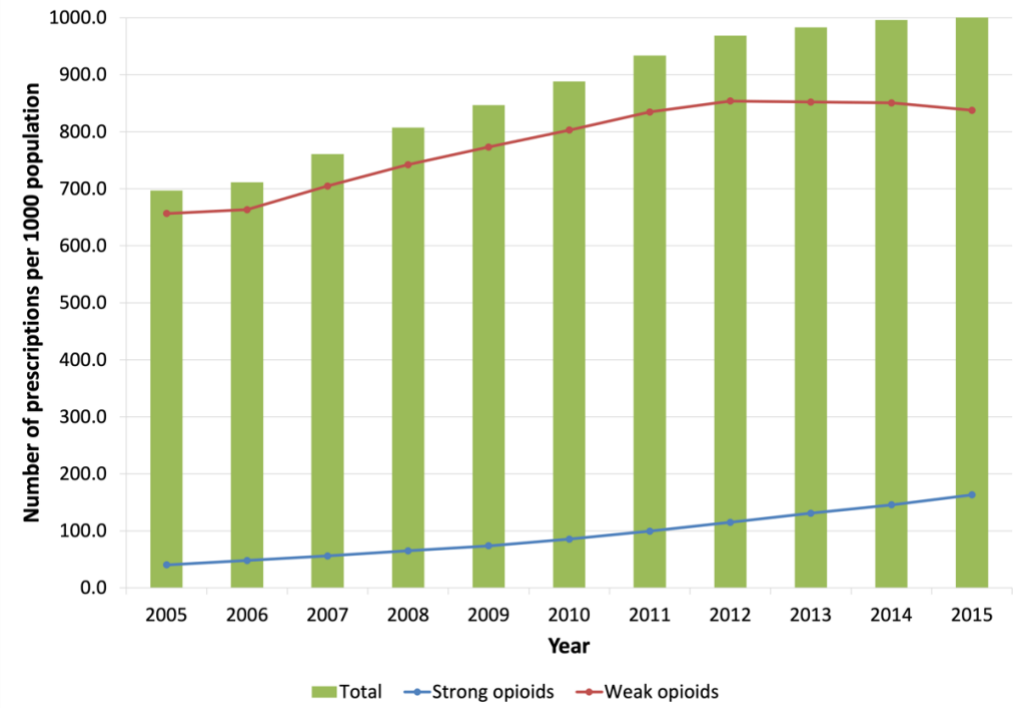


Figure 3.1: Trends in number of prescriptions per 1,000 issued between 2005 and 2015, stratified by opioid-type

Weak opioid prescribing covered 89.3% (20,350,394 of 22,786,565 prescriptions) of all opioid prescribing between 2005 and 2015. Whilst annual prescription

numbers peaked in 2012, the percentage of weak opioid prescriptions as a percentage of all opioid prescriptions being issued, reduced annually. Strong opioids accounted for 10.7% of all opioid analgesic prescriptions issued between 2005-2015. However, the percentage of total prescribing accounted for by strong opioids rose from 5.8% (40.2 from 696.8 total prescriptions per 1,000 population) to 16.3% (163.1 from 1000.7 total prescriptions per 1,000 population) over that time.

3.5.3 Trends in prescribing by gender

Women comprised 56.4% of the total number of people receiving opioid prescriptions. Just under 30% percent more individual women (n=620,288) than men (n=478,738) received opioid prescriptions between 2005 and 2015. On an average basis however, 60% of people receiving prescriptions each year were women (Appendix B).

One and a half times more prescriptions for opioid analgesics were issued to women than men between 2005 and 2015 (Table 3.2 and Appendix B). Over the study period, women received 13,992,935 prescriptions, significantly more than the 8,793,630 received by men (Mann-Whitney U test, U=121.00, SE=15.23, $p<.001$, $\eta^2=0.72$, $d_{Cohen}=3.19$).

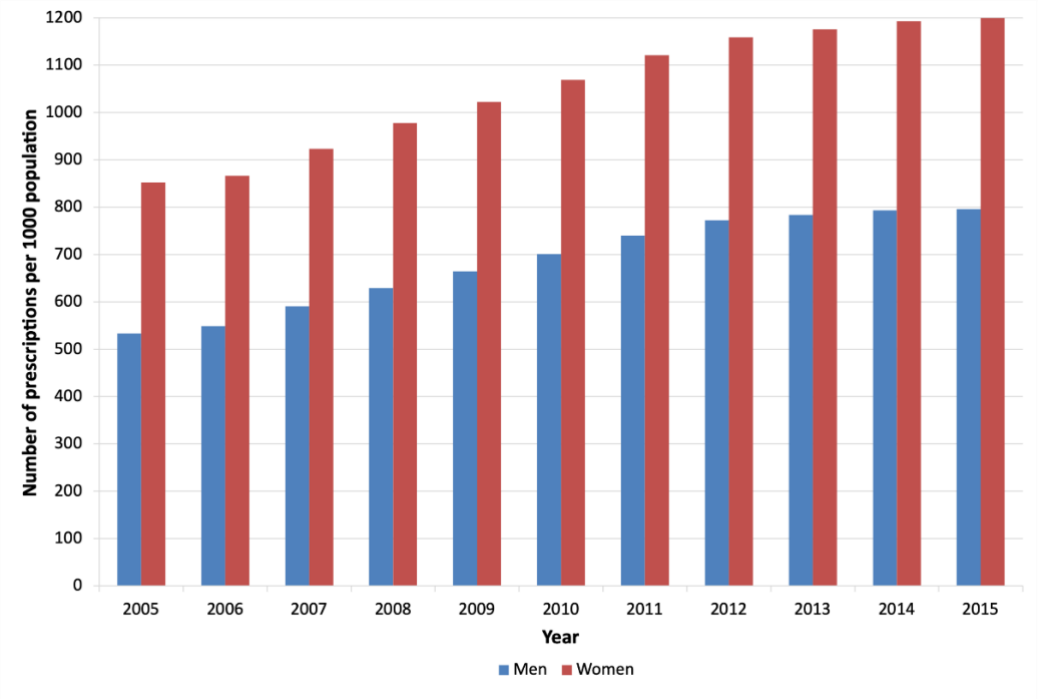


Figure 3.2: Trends in opioid analgesic prescribing rate 2005 to 2015, stratified by gender

Women steadily received the same proportion of all prescriptions throughout the study period, accounting for around 60% of all opioid prescriptions issued in total, consistent with results already set out (Figure 3.2).

Table 3.2: Gender trends in opioid prescription rates during the study period, 2005 - 2015

	Per 1,000 gender population		Change in variable	Percentage change (%)	Spearman's r p-value
	2005	2015			
Total					
Men	533.1	795.6	262.5	49.3	>.999, p<.001*
Women	852.6	1199.6	347.0	40.7	>.999, p<.001*
Weak opioid					
Men	496.4	665.6	169.2	34.1	0.909, p<.001*
Women	809.1	1004.3	195.2	24.1	0.909, p<.001*
Strong opioid					
Men	36.6	130.0	93.4	255.2	>.999, p<.001*
Women	43.5	195.2	151.7	348.7	>.999, p<.001*

*p<0.05=statistically significant. Annual data Appendix B.

Women and men saw year-on-year increases in the number of opioid prescriptions issued between 2005 and 2015, although the rates of increase were reducing towards the end of the study period (**Error! Reference source not found.**).

Weak opioid prescribing rates rose more for men than women in the time period examined. As previously illustrated (Figure 3.1), there were peaks in prescribing

rates of weak opioids for men and women in 2012, followed by small reductions in annual numbers (Appendix B).

As was seen with overall prescribing rates, women received around 60% of all weak opioid prescriptions issued over the study period. Predictably, women received significantly more prescriptions than men for weak opioids (Table 3.2), as confirmed by a Mann-Whitney U test (U=121.00, SE=15.23, p<.001, η^2=0.72, d_{Cohen}= 3.19).

Very large increases were observed in strong opioid prescribing rates for men and women between 2005 and 2015 (Table 3.2). Spearman's Rho correlations were very strong for both genders (r>.999, p<.001), demonstrating a clearly positive upwards trend over time (Table 3.2).

Year on year increases in strong opioid prescribing rates were noted throughout the study period although for both genders, the rate of increase slightly slowed in the second half of the study period (Appendix B). Between 2005 and 2015, prescribing rose 83.7% (from 36.6 to 69.0 prescriptions per 1,000 population) for men and 91.8% (from 43.5 to 101.0 prescriptions per 1,000 population) for women. In the second half of the period, 2010 to 2015, men's strong opioid prescribing rates rose 81.7% (from 69.0 to 130.0 prescriptions per 1,000 population) and for women it was 87.3% (from 101.0 to 195.2 prescriptions per 1,000 population) (Appendix B).

3.5.4 Prescribing by age

Using the age on the date of prescription, the average age for people receiving an opioid prescription for any indication was 55.2 years (SD=18.0, range 18-110 years). In individual terms, people aged 45 to 64 years, were the most represented age group between 2005 and 2015 (Figure 3.3) with nearly half a million more people in that age-group receiving opioid prescriptions than in any other.

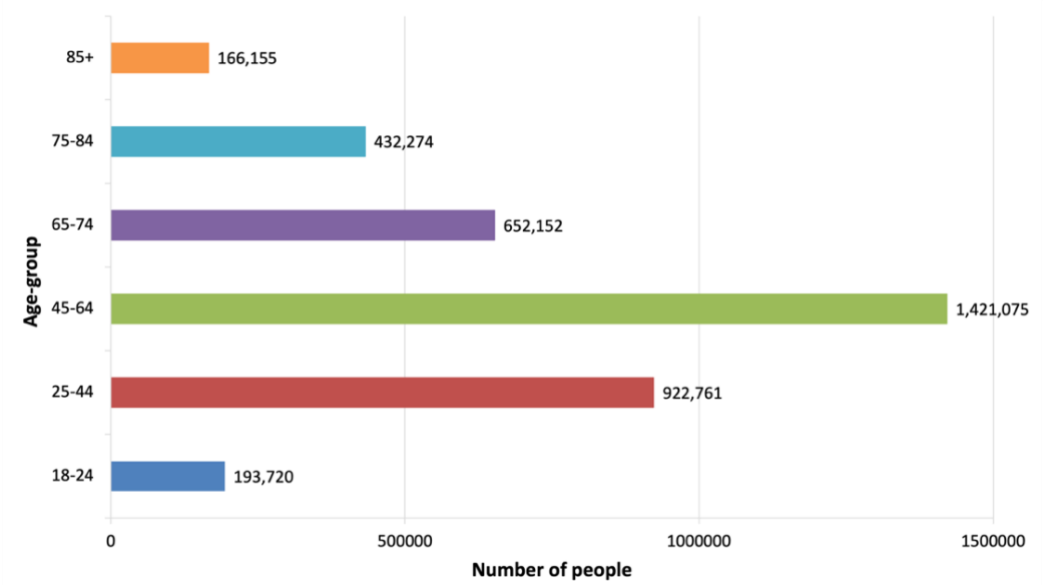


Figure 3.3: Number of people receiving opioid analgesic prescriptions between 2005 and 2015, stratified by age-group

People aged 65 years and above between 2005 and 2015, received more prescriptions than those in lower age-groups (Table 3.3). Eleven times more prescriptions (per 1,000 population) were issued to people aged 85 years and over, compared to those aged between 18 and 24 years old (Appendix B). In respect of number of prescriptions issued there was a 2-times difference between the oldest and youngest age-groups, which points to disproportionate prescribing by age (**Error! Reference source not found.**). Increases in the rates of prescribing (prescriptions per 1,000) were noted for all age groups over the study period, although the youngest age-group (18 to 24 years) demonstrated only moderate correlation compared to strong correlations noted in all other age-groups (Table 3.3).

Table 3.3: Change in rates of prescribing (adjusted to population) issued 2005 to 2015, stratified by age-group

Age group (years)	Per 1,000 age-adjusted population		Change in variable	Percentage change (%)	Spearman's r p-value*
	2005	2015			
Total					
18 – 24	119.1	123.8	4.7	4.0	.418, p=0.201
25 – 44	394.7	598.5	203.8	51.6	.991, p<.001*
45 – 64	822.1	1229.0	406.9	49.5	>.999, p<.001*
65 – 74	1211.8	1421.5	209.7	17.3	.909, p<.001*
75 – 84	1271.1	1596.2	325.1	25.6	.982, p<.001*
85+	1359.1	1573.0	214.0	15.7	.945, p<.001*
Weak opioid					
18 – 24	110.9	114.2	3.2	2.9	.418, p=0.201

25 – 44	362.2	489.8	127.6	35.2	.873, p<.001*
45 – 64	773.8	1010.1	236.3	30.2	.873, p<.001*
65 – 74	1162.1	1229.8	67.8	5.8	.582, p=0.060
75 – 84	1213.7	1374.8	161.1	13.3	.873, p<.001*
85+	1284.8	1301.3	16.5	1.3	.791, p<0.01*
Strong opioid					
18 – 24	8.1	9.7	1.5	18.6	.041, p=0.905
25 – 44	32.5	108.7	76.2	234.1	>.999, p<.001*
45 – 64	48.4	219.0	170.6	352.8	>.999, p<.001*
65 – 74	49.8	191.6	141.9	285.0	>.999, p<.001*
75 – 84	57.4	221.4	164.0	285.9	>.999, p<.001*
85+	74.3	271.8	197.5	265.8	>.999, p<.001*

in annual prescription numbers was noted in the 25 – 44 years group (Table 3.3). The second largest increase was observed in the 45 to 64 years age group, although there were twice as many prescriptions issued compared to the 25 – 44 years group over the period examined (Table 3.3).

Prescriptions for people aged 65 years and older accounted for 46.2% (8,707,403 of 22,808,675) of the total number of prescriptions issued between 2005 and 2015. However, when adjusted to each age-group population this changed to 71.3% of prescriptions per 1,000 population issued within to people aged 65 years and above**Error! Reference source not found.**. Based on prescriptions per 1,000 age-adjusted population data, the group which had the highest rate of prescribing was aged 85 years and older.

The trend in the number of weak opioid prescriptions issued by age-group followed a similar trend to those seen in the number of people receiving prescriptions (Appendix B). The largest increase was in the 25 to 44 years age group, as with the overall trend.

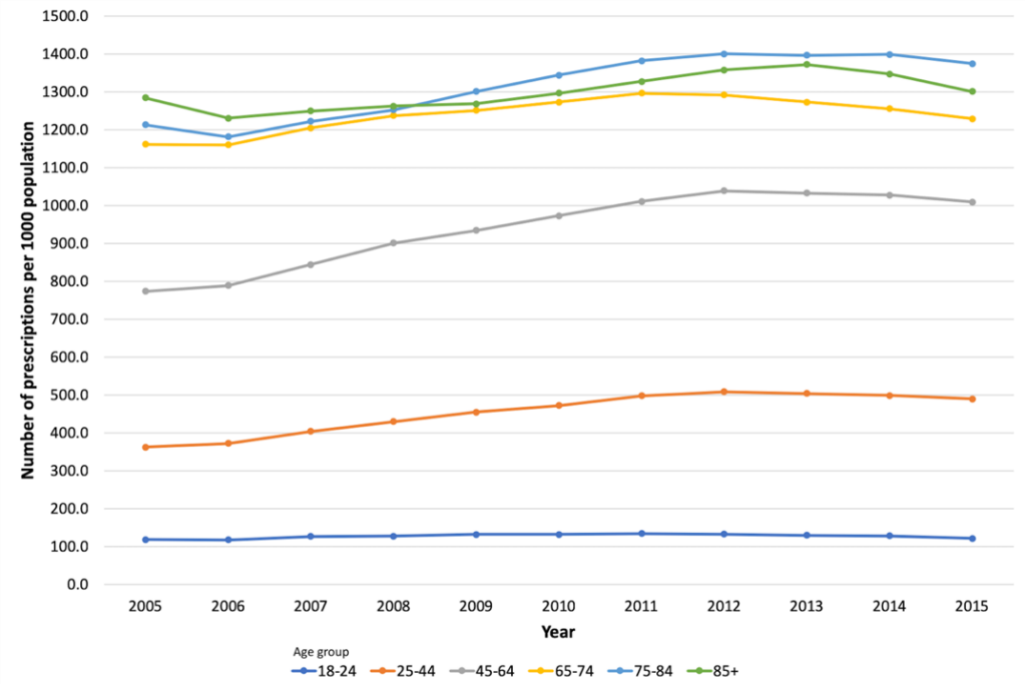


Figure 3.4: Trends in the number of weak opioid prescriptions issued between 2005 and 2015 and stratified by age-group. Data displayed by number of prescriptions per 1,000 age-group adjusted population per year

A Kruskal-Wallis test demonstrated a significant difference (H= 58.66, p<.001, η^2=0.89, d_{Cohen}= 5.82) between the number of prescriptions issued to the various age-groups over the study period. Dunn's pairwise tests, and Bonferroni corrections confirmed significantly more weak opioid prescriptions were issued to individuals aged 45 years and above, when compared to the 18- to 24- year group (Appendix B). Significantly fewer prescriptions were issued to 25- to 44-year-olds compared to those aged 75 years and over. No other statistically significant differences in the rates of weak opioid analgesics were observed between age groups (Appendix B).

Strong opioid prescribing rates more than tripled in all age-groups other than the youngest group (18 – 24 years) (Figure 3.5) over the 11 years analysed. The largest percentage increase was noted in the 45 to 64 years age-group (Table 3.3). Differences were tested using a Kruskal-Wallis test and were statistically significant (H= 51.38, p<.001, η^2=0.77, d_{Cohen}= 3.69). The youngest age-group (18-24 years) were confirmed to have significantly fewer prescriptions than all age-groups age 45 years and over. The older two age-groups were confirmed to have significantly more prescriptions than 24-44 year olds also (Appendix B).

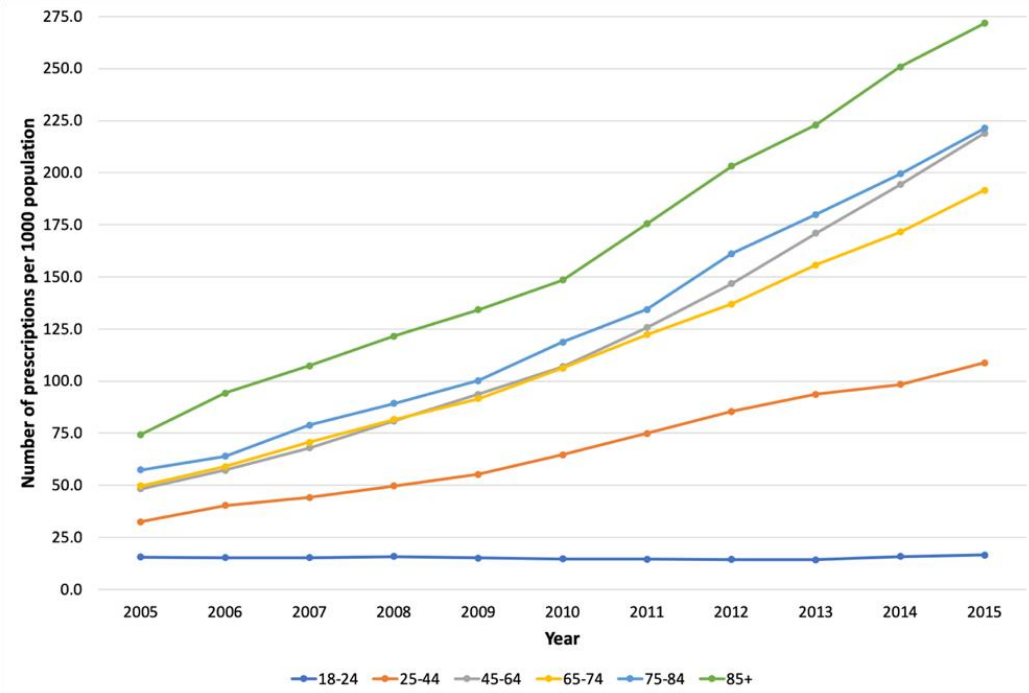


Figure 3.5: Trends in the number of strong opioid prescriptions between 2005 and 2015 and stratified by age-group. Data displayed by number of prescriptions per 1,000 age-group adjusted population per year

Two thirds of strong opioid prescriptions were issued to people aged 65 years and above (based on population-adjusted data) (Figure 3.5) between 2005 and 2015. Over the 11 years of the study, 28% more prescriptions were issued to people in the age-group aged 85 years and over than the group with the next highest number of prescriptions, aged 75 – 84 years (Figure 3.5).

3.5.5 Prescribing persistence

Between 2005 and 2015, there were 4,308,035 opioid prescribing events in the 345 SAIL registered practices (Table 3.4). Of these, 4,095,952 (95%) events had a prescribing persistence of 31 days or less, with 3,978,480 (92.4%) events classified as single events, where a second prescription was not issued within 31.5 days of the first.

When all prescriptions were included in the analysis, average prescribing persistence was 8.6 ± 63.3 days (Table 3.4). Removing all single prescriptions (where another was not issued within 31 days), average persistence duration increased to 94.7 ± 189.8 days.

For the 11 years analysed, 99,699 (3.8 events per 1,000 population) prescribing events occurred with a persistence of more than 3 months (≥91 days) and an average prescribing period of 265.7 ± 317.1 days (Table 3.4). Of those, 46,378 (1.8 events per 1,000 population) had a prescribing persistence of over 6 months (≥181 days) and an average period of 423.9 ± 410.7 (SD) days.

There were 4,837 (0.2 events per 1,000 population) prescribing periods of more than 2 years (>730 days, mean average 1356.9 ± 712.2 days), 856 (0.03 events per 1,000 population) periods of more than 5 years (>1825 days, mean average 2660.5 ± 645.7 days) and 110 periods that extended over 10 years (>3650 days, mean average 3794.1 ± 84.8 days).

Table 3.4: Demographics for prescribing persistence adjusted to population

Mean data for period 2005-2015	**Period of prescription persistence**			
	Total	≤31 days	≥91 days	≥181 days
Number of events	4308035	4095952	99699	46378
Mean prescription persistence (days) ± SD	8.60 ± 63.309	9.4 ± 4.726	265.73 ± 317.085	423.88 ± 410.739
Range	0-3951	0-31	91-3951	181-3951
Number of events per 1,000 population	165.1	157.0	3.8	1.8
Gender				
Male	137.0 (41.6)	129.9 (41.5)	3.2 (42.6)	1.5 (42.2)
Female	192.2 (58.4)	183.1 (58.5)	4.4 (57.4)	2.0 (57.8)
Last opioid in prescription period				
Strong	6.7 (4.1)	6.1 (3.9)	0.3 (8.4)	0.2 (9.2)
Weak	158.4 (95.9)	150.9(96.1)	3.5 (91.6)	1.6 (90.8)
Deprivation quintile WIMD2011				
WIMD1	209.2 (26.4)	197.3 (26.2)	5.7 (31.3)	2.7 (31.7)
WIMD2	173.6 (21.9)	164.7 (21.8)	4.3 (23.2)	2.0 (23.9)
WIMD3	165.8 (20.9)	157.7 (20.9)	3.8 (20.7)	1.8 (20.9)
WIMD4	128.7 (16.2)	123.4 (16.4)	2.4 (13.1)	1.1 (12.7)
WIMD5	115.7 (14.6)	110.9 (14.7)	2.1 (11.6)	0.9 (10.9)
Recorded diagnoses				
Big six non cancer pain	119.7 (72.5)	113.6 (72.3)	2.9 (74.8)	1.3 (74.6)
Depression/anxiety	47.5 (28.8)	45.0 (28.7)	1.2 (31.2)	0.6 (32.0)

3.6 Discussion

3.6.1 Summary and reflection on findings

In answer to the study question, 'how has opioid prescribing changed over time?' the results presented in this chapter demonstrate that between 2005 and 2015, the number of prescriptions for opioids in Wales increased considerably (Section 3.2). Large rises in the number of people being issued prescriptions were also observed (Appendix B). Even within the context of a substantial overall rise, the huge percentage increases in prescriptions for strong opioid analgesics such as morphine, oxycodone and fentanyl were striking. Many more women received prescriptions than men for the duration of the data collection period, with correspondingly higher numbers of prescriptions for all classes of opioids. Opioid prescribing rates also increased with age, again with trends consistent for both weak and strong opioid analgesics. Consequently, the study question of whether gender and age might affect prescribing can be answered in the affirmative.

It may be assumed that higher rates of prescribing in women compared to men is linked to their increased reporting of pain. There may be, as discussed earlier (Section 1.8), reasons women experience higher levels of pain and as a result, be offered opioid analgesics more frequently than their male counterparts (Section 3.6.5). Further analysis to examine differences in oral morphine equivalent dosing, between genders was conducted as part of this thesis and will be presented in Chapter 5. Pain prevalence has been shown to increase with age (Section 1.9), as does the occurrence of disease states such as musculoskeletal conditions, which, are also associated with pain (Ali et al. 2018). Consequently, it may not be entirely surprising to see more opioid prescriptions issued to the oldest people in the population. However, with increasing age, there is also a tendency to observe multiple morbidities and polypharmacy, which can make older people more susceptible to the adverse effects, interactions and harms associated with opioid analgesics, at any dose (Section 1.7). The much higher rates of prescribing of strong opioids, once again, are perhaps of greatest concern in an aging population. Of interest is the large rise in prescribing rates in people of working age. It raises the question of whether the rise of opioid

analgesic prescribing is associated with changes in employment due to ill-health or if opioids allow people to remain in work (Hanna et al. 2020).

Prescription persistence was a measure devised for this study in the absence of information required to undertake an accurate calculation. Using an estimation there was a trend of increasing prescription persistence between 2005 and 2015. In other words, the data suggests more people are taking opioid analgesics for longer periods of time. Age did not appear to be a major factor in prescribing persistence, with little difference between all but the youngest age-group (18 – 24 years). Whilst not included in the results shown in this chapter, analysis of prescribing persistence demonstrated people residing in areas of greatest deprivation were exposed to opioid analgesics for greater durations than those in areas with better socioeconomic conditions (Appendix G). Persistent durations of opioid use were also observed more frequently for people aged over 45 years. The implications of extended duration of use are significant clinically, given the wide range of harms opioids can cause. The prevalence of long-term prescribing in people of working age is something requiring further investigation, as repercussions in workforce availability have farther reaching consequences, economically as well as on healthcare services. Opioid analgesics have not been shown to be effective for most people. So, there are questions arising from this finding in terms of how people receiving opioid analgesics are being reviewed and advised in all healthcare settings across Wales.

3.6.2 Comparison of general opioid prescribing trends in the UK

A variety of different data collection methods have been used to examine opioid prescribing across the UK, making direct comparisons less straightforward (Zin et al. 2014; Mordecai et al. 2018; Torrance et al. 2018; Jani et al. 2020a). Zin et al. (2014) analysed changes in the number of prescriptions issued for four strong opioid medicines (buprenorphine, fentanyl, morphine, and oxycodone) between 2000 and 2010. Mordecai et al. (2018) looked at a larger range of opioid medicines but used trends in oral morphine equivalent quantity as the measure of change over a 43-month period (Mordecai et al. 2018). Recently, Jani et al.

(2020) published prescribing trends in the UK between 2006 and 2017. The analysis included prescribing rates for individual opioid analgesics with for example, a 5-fold increase in codeine prescribing in that time (Jani et al. 2020). However, the trends in opioid prescription numbers noted in this study corroborate those observed in other UK-based analyses. Curtis and colleagues (2019) undertook a large review of opioid prescribing trends, using nationally available prescribing data from England (Curtis et al. 2019). Between 1998 and 2016, a 34% (from 568 to 761 prescriptions per 1,000 population) increase in the number of oral and transdermal opioid prescriptions dispensed was found. Substantial prescribing variation across the country was described (Curtis et al. 2019), contributing to a percentage increase lower than that observed in Wales. A similar trend was observed in Tayside, Scotland, where a 29% increase (8.5% RR to 11.0% RR standardised data) in opioid prescribing was reported between 1995 and 2010 (Ruscitto et al. 2015). These results are in line with the 43.9% rise in prescription numbers (per 1,000 population) reported, albeit the increases in Wales were observed over a shorter time period. Of interest is the peak in overall opioid prescribing rates noted in 2012, which was a similar finding observed by Jani (2020). In that study of UK-wide opioid analgesic prescribing rates between 1998 and 2016 (Curtis et al. 2019), tramadol, oxycodone and fentanyl prescribing were noted to begin to decline in 2012 although codeine and morphine continued to increase (Jani et al. 2020).

Primary care prescribers frequently express concern about prescribing strong opioids in particular (McCrorie et al. 2015; Kinnaird et al. 2019), which perhaps, contradicts the trends observed in the data. Furthermore, these rises have been noted over a period where evidence to support using opioids in long-term pain was rather rapidly falling away. Questions of how changes in practice or evidence for prescribing choices are communicated and practitioners' compliance with best practice is monitored are also relevant in this situation. The influence of guidance and legislation on opioid prescribing in Wales is examined in Chapter 6.

Similar increases in opioid prescribing have been reported elsewhere in Europe (Gustavsson et al. 2012; Bosetti et al. 2019), North America (Silversides 2011; Kenan et al. 2012) and Australia (Karanges et al. 2016; Wagemaakers et al. 2017). It would be wrong however, to assume these trends are mirrored everywhere, even within recognised international boundaries. A Portuguese study, for example, suggested only a small percentage (4.37%) of people living with pain were using opioid analgesics as part of their management, in spite of the majority of people (76%) questioned using analgesic medicines (Azevedo et al. 2013). Whilst an increase in analgesic prescribing has been recorded in France, ranking it third for overall consumption, in comparison to other European countries, they have amongst the lowest strong opioid prescribing (Hider-Mlynarz et al. 2018).

At the end of the TOPAS study period (2015), the UK was observed to have the highest opioid prescribing in Europe for both weak and strong opioids. This was accounted for by high rates of codeine and morphine prescribing (Hider-Mlynarz et al. 2018), consistent with prescribing patterns noted in Wales at that time (see Chapter 5). European data also identified the UK as having the highest rates of high-risk (illicit) opioid use in the Europe (European Monitoring Centre 2020). However, the International Narcotics Control Board (INCB) released data which placed the UK 16th from 22 European countries in terms of opioid consumption (DDD per million inhabitants per day) (International Narcotics Control Board 2016). Consumption of opioids (morphine equivalent in mg/capita) worldwide placed the UK around the middle of countries whose data was presented but still much lower than North America, Australia and Germany (International Narcotics Control Board 2016). These differences raise questions which warrant further investigation. Cultural differences in pain perception and the necessity of medicines in its management may play a part in decision making around prescribing (Meyer et al. 2020). This is likely to affect practitioners and individuals who might receive prescriptions, as well as determining whether other, non-pharmacological management options are available. Large differences in healthcare systems across the world also impact on service development and

the role that different healthcare professionals are able to play in providing and reviewing pain management and prescribing. Meyer et al (2020) examined some of these issues in the context of opioid prescribing in Rhode Island (Meyer et al. 2020). The suggestion was that the USA should consider moving towards a more 'European' model of optimising health and wellness rather than simply addressing symptoms and conditions within a purely medicalised system. European controls on advertising pharmaceutical products was cited as one difference that was likely to influence patient-demand for medication and which has been demonstrated to have had direct impact on prescribing levels in the USA (McGreal 2018; Marks 2020; Meyer et al. 2020).

3.6.3 Weak versus strong opioids

An overall increase in all opioid types was observed across the 11 years of the study although rates of increase began to slow from around 2012 onwards. The reduced pace of growth could be traced back to reductions in prescribing of particular drugs, of note tramadol and fentanyl (Chapter 5). This finding was mirrored by a study of UK-wide opioid prescribing where a reduction in tramadol, oxycodone and fentanyl was observed from 2012 onwards (Jani et al. 2020). A reduction in the overall rate of opioid prescribing was reported in England between 2016 and 2017 (Curtis et al. 2019). Despite the deceleration of prescribing, the disproportionate increases in 'strong' opioid prescribing as a percentage of all opioids throughout this study mirrors observations of others who have monitored opioid prescribing from the early 2000's onwards (Torrance et al. 2018; Green et al. 2019). An increase of 554% (from 0.13% to 0.85% of people receiving at least one opioid prescription) in the proportion of patients receiving strong opioid prescriptions was reported in a population of people accessing primary care services in Leeds and Bradford between 2008 and 2012 (Foy et al. 2018). Whilst this remains a small percentage of opioid users overall, the relative size of increase over 4 years reflects findings of other studies where strong opioid prescribing was examined. Zin et al (Zin et al. 2014), examined strong opioid prescribing in isolation and reported an 80.4% (from 1.8 to 9.2 patients per 1,000) increase in the number of people issued strong opioid

prescriptions in a UK population (predominantly in England) between 2000 and 2010. This was a greater increase than the 66.9% seen in Wales between 2005 and 2015. A larger proportion of the Welsh population was included in this analysis relative to that evaluated by Zin and colleagues however, which may account for some differences.

3.6.4 People versus prescriptions

Zin et al. (2014) described a 411% increase in the number of people (from 1.8 to 9.2 people per 1,000) receiving prescriptions and a 60% increase in prescriptions (from 6.0 to 9.5 prescriptions per patient) for strong opioids between 2000 and 2010 in the UK. Using the same measures, this study observed a 202% increase (from 4.4 to 13.3 people per 1,000 population) and a 35% rise (from 9.1 to 12.3 prescriptions per patient) in strong opioids over a similar period. Whilst the percentage increases in this study were lower, it points towards a higher overall level of strong opioid prescribing in Wales than noted in the predominantly English data (Zin et al. 2014). The implication of a large increase in the number of people compared to prescriptions per person suggests that the majority of prescriptions issued are short-term (e.g., for acute pain indications).

Comparisons can be drawn with similar findings elsewhere in Europe (Rosner et al. 2019). A systematic review of prescribing trend studies from Germany did not establish a percentage increase in annual prescription numbers but highlighted the biggest reported increase in prescription prevalence being 37% between 2000 and 2010 (Rosner et al. 2019). In Norway between 2004 and 2007, a 9% increase in the number of people without cancer, receiving opioids was observed. Numbers of prescriptions were not measured in the study however (Fredheim et al. 2010). Regional variation in people and prescriptions were reported in Germany, with a north-south divide described (Rosner et al. 2019). Similar regional variances were observed in Wales, with the seven health boards showing slightly differing trends (Appendix I).

3.6.5 Gender differences in opioid prescribing

The number of women compared to men across all age-groups increased in terms of receiving prescriptions and also the annual prescriptions issued. Similar findings have been noted by other UK-based studies (Zin et al. 2014; Ruscitto et al. 2015). In England and Scotland, greater differences between men and women were noted for the increases in strong opioid prescribing over the respective study periods (Zin et al. 2014; Ruscitto et al. 2015), which this study corroborated. Long-term prescribing rates for opioid analgesics in England were shown to be consistently higher in women and increased more between 2002 and 2013 than for men (Bedson et al. 2016), again corroborated by the TOPAS study. Other UK studies have documented women receiving opioids in greater numbers than men but without examining changes in those figures over time (Todd et al. 2018; Torrance et al. 2018). Data from the USA have shown large reductions in overall rates of opioid prescribing over the last 10 years (IQVIA 2020). Between 2008 and 2018, based on data from 92% of retail pharmacies in the USA, reductions in the number of men and women receiving opioids were around 30% overall although statistically higher numbers of women consistently filled prescriptions (Schieber et al. 2020). The largest differences between genders was in the youngest age-group examined (20-24 years), where twice as many women as men filled prescriptions (Schieber et al. 2020). Whilst studies consistently report proportions of men and women included data trends by gender are much less frequently reported. Concerns about gender-disparities in accessing support for painful conditions have been highlighted recently in the UK (Barnett 2020; Connolly 2020; Marsh 2021; Warraich 2021), focussing on gynaecological-related pain in particular. However, gender differences in presentation and prevalence of other pain-related conditions have been observed including chronic back pain, where in women, associations with the menstrual cycle and age-associated changes in hormone levels may account for increased prevalence (Fehrmann et al. 2019; Rathbone et al. 2020). Variation between men and women, in response to pain rehabilitation have also been reported (Rovner et al. 2017) and could have implications for analgesic use as

well. Further research into differences in opioid and analgesic prescribing between men and women is needed. The use of analgesics needs to be placed in the context of underlying causes of pain, genetic and hormonal variation and emotional or psychological differences between genders.

3.6.6 Age differences in opioid prescribing

The study data demonstrated that people in the oldest age-groups (85+ years) had the highest rates of prescribing for all types of opioids between 2005 and 2015. Long-term prescribing in an English primary care population observed that people aged 65+ years were more likely to receive an opioid prescription, and this was a consistent pattern noted over 11 years (Bedson et al. 2016). As prescribing persisted, the percentage of younger people maintained on opioids increased and was not dissimilar to that seen in the older group (Bedson et al. 2016). However, a number of UK studies have shown similar results, with higher rates of prescribing noted in older age groups (Zin et al. 2014; Ruscitto et al. 2015; Torrance et al. 2018). Jani et al. (2020) examined prescribing trends in England which, whilst not presenting age-group trend analysis, did show the factor with greatest odds ratio for long-term opioid use was being age 75 years and over (Jani et al. 2020), which findings presented here would corroborate. As in the TOPAS study, the likelihood of receiving strong opioid prescriptions also increased with age with 31% of strong opioids initiated in people aged 85 years and over (Jani et al. 2020).

An increase of 171% (from 4.2% to 11.4% of patients) in the percentage of people aged 65 years and older receiving opioid prescriptions was observed between 2005 and 2017 in the Netherlands. The percentage of strong opioid prescribing increased 438.5% (from 1.3 to 7.0% of prescriptions) The oldest patients (aged 85+ years) were more likely to be given a prescription for a strong opioid, with 40% having them prescribed for 3 months or more (Weesie et al. 2020). The increases reported appear much larger than those described in the TOPAS data. However, the overall trends are similar, not least with strong opioid prescribing increasing most in the oldest population. In the Weesie et al. (2020)

study, cancer was the principal reason for opioid prescribing in the 85+ years group (Weesie et al. 2020). This study specifically looked at non-cancer prescribing yet demonstrated similar patterns. High levels of opioid analgesics in older, more metabolically vulnerable people is a cause of concern due to the potential for inadvertent toxicity and overdose (Huang and Mallet 2013; Gazelka et al. 2020).

Despite overall reductions in percentages of age-grouped adults receiving opioid analgesics in the USA , the smallest reductions were observed in people aged 45 years and above. The number of prescriptions per person in those groups barely changed between 2008 and 2018. People aged 55-64 years actually had a small increase (Schieber et al. 2020) which corresponds to data presented here, which, revealed that some of the largest increases in prescribing were noted in the 45-64 years age-group, whilst overall, the highest rates were maintained in the oldest age-groups.

3.6.7 Prescribing persistence or duration

By far the majority of opioid prescribing throughout this study (95%), was short-term with prescriptions not repeated within 31 days. This accords with Chevalier et al.'s (2014) observations of 50.5% of opioids being prescribed for less than <31 days, in a primary care population in the UK (Chevalier et al. 2014). In Chevalier et al.'s study, people were excluded from analysis once their indexed prescribing period finished, whereas this study allowed repeated presentations by individuals, with a break of more than 31 days between prescriptions considered a new prescribing period. This may have led to intermittent but persistent prescribing being observed as short-term when it actually covered longer periods. This is a potential limitation of any research in this area (Bedson et al. 2016; Jani et al. 2020). The only accurate method to determine longevity of using opioids would be to take a history from each individual patient. Consequently, all measures of prescription persistence or opioid use are essentially estimations (Zin et al. 2014; Lalic et al. 2018). Using a method to determine persistence used

by other researchers, was decided to provide a reliable measure for this study (Chang et al. 2018).

People with prescription persistence of more than six months constituted 1% of this study's population with an average of 424 days exposure. The percentage of long-term users appears low in comparison to other study's findings. Chevalier et al. (2014) noted 21% of study participants had chronic opioid exposure with an average 170 days continuous use, using similar criteria as this study but where the population was on average nearly 10 years older (Chevalier et al. 2014). In the same study, chronic users made up 6.3% of the German cohort, with a similar average age to their UK counterparts with an average continuous prescribing duration of 567 days (Chevalier et al. 2014). In an Australian population, 2.6% (~430,000 people) met the criteria of persistent opioid use when a group-based trajectory model (GBTM) was used over a 12-month period (Lalic et al. 2018). The GBTM method avoids setting explicit criteria for persistence. Instead, it uses a probability calculation based on patterns of prescribing in the 12 months after the first prescription (Lalic et al. 2018). Kern et al. (2015) noted chronic use (>183 days) composed 6.8% of prescribing in an American population (~256,000 people), substantially higher than in the analysis presented here, where the same persistence criteria was used (Kern et al. 2015). It was also higher than an earlier American study which had an average 2.7% of supply >181 days over 5 years (Sullivan et al. 2008), perhaps reflecting the rapid rise in opioid use across America since the early 2000s. Bedson et al. (2016) examined trends in long-term prescribing (more than 3 prescriptions in a 90-day period) in a population with musculoskeletal conditions, between 2002 and 2013, a similar time period to this study. Overall, a 38% increase in the incidence of long-term prescribing was reported, (Bedson et al. 2016). This was much lower than noted in the TOPAS data, where a 508% (from 1736 to 10,560 events) increase in the number of prescribing events with a duration of more than 6 months was observed between 2005 and 2015 (Appendix G).

The GBTM method adopted by Lalic's group aims to overcome the need for explicit criteria to define persistence (Lalic et al. 2018). Prescribing persistence has been differently defined by researchers. Durations of <30 days, 31-90 days, 91-179 days and >180 days have all been used in the literature to define periods of interest. Generally, durations over 90 days may be referred to as chronic or long-term prescribing (Portenoy and Foley 1986; Sullivan et al. 2008; Kern et al. 2015; Bedson et al. 2016; Jain et al. 2018).What all these studies demonstrate is that there is no clear definition of prescribing persistence. Further research would be beneficial to determine consensus on what measure could be used in Wales, to consistently measure prescribing persistence. Duration of use appears to be as important a factor in developing long-term harms as dose (Scherrer et al. 2016; Mundkur et al. 2017; Salas et al. 2020) and therefore, even if the overall number of prescription reduces, prescribers must still be vigilant for long-term use.

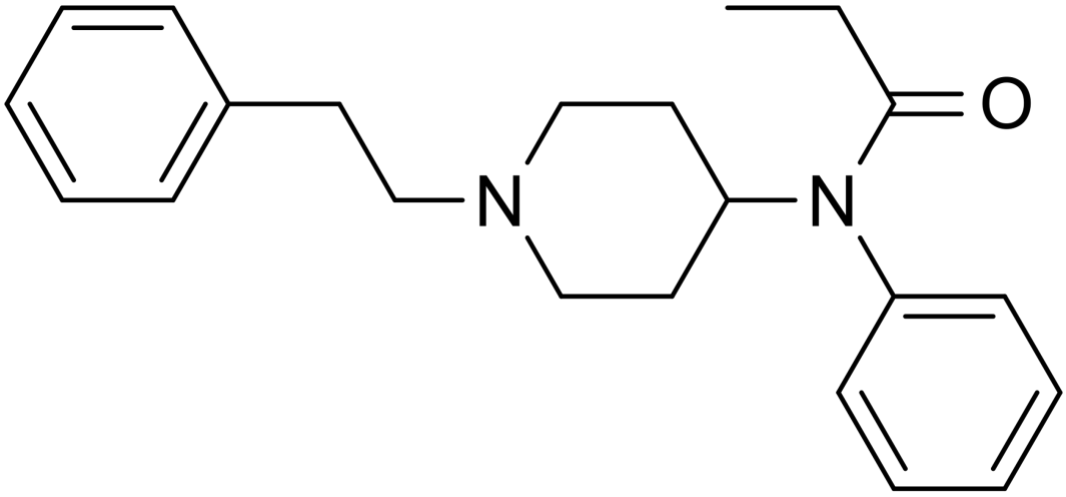
3.7 Conclusion

The data presented in this first results chapter, shows large increases in opioid prescribing in Wales between 2005 and 2015. Over the 11 years analysed, more people received a greater number of prescriptions for opioid analgesics each year. Whilst there was a signal that increases in overall prescribing rates were starting to slow and reduce towards the end of the study period, strong opioids, often associated with greater risks of harm and misuse, were continuing to rise.

Opioid prescribing appears to be directed disproportionately towards women, who receive substantially more prescriptions than their male counterparts. There is evidence women present more frequently with pain and also, that they respond more positively to opioids. It is probably insufficient to explain the difference in rates of prescribing between men and women, however. Subsequent chapters will return to gender discrepancies as other aspects of opioid prescribing are examined.

People aged 45 years and above received most prescriptions. This might appear easily explained as pain reporting increases with age and this is well established. Consequently, perhaps it should not be surprising most of the prescribing is observed in older people. The risks of opioids in older populations are significant, however. They are likely to contribute to morbidity and even mortality in some cases, especially when combined with other high-risk medicines. This study is the first to attempt to examine prescribing persistence in Wales, given its growing importance as a risk factor for opioid-induced harm. The data signals the duration of use is rising in all ages and genders receiving opioid prescriptions. Rates of opioid prescribing in working aged people are a concern. If greater numbers are being initiated on opioid analgesics that persist for longer periods of time, this has potentially serious implications for the general health, wellbeing, and productivity of the population.

Chapter 4
Trends in prescribing by socio-economic deprivation



"…… any claim that the NHS has achieved its aim of providing equality in medical care is an illusion. In fact, absolute equality could never be achieved under any system of medical care, education, or other essential service to the community. The motives for suggesting otherwise are political and ignore human factors"
British Medical Association, 1971

Chapter 4 – Trends in prescribing by socio-economic deprivation

4.1 Chapter overview

The social and economic burden of pain and the role of opioids in managing it was considered in Chapter 1. Alongside that, population health in Wales and how socioeconomic deprivation impacts upon it was discussed. Chapter 2 set out the use of linked-data and the main methods used to extract and analyse data for the project. Chapter 3 set out the overarching trends in opioid prescribing across Wales, stratified by drug-group, gender, and age-group. Thus far, a significant increase in opioid prescribing across Wales, between 2005 and 2015 has been revealed. The rates of prescribing rose most sharply for strong opioids such as morphine and oxycodone. Opioid prescribing has been shown to be more prevalent in women than men and for people aged 45 and over in particular. Chapter 4 examines in more detail, trends in opioid prescribing in areas which have differing levels of socioeconomic deprivation. Initially, links between pain and deprivation will be considered, as a means of explaining the data explored in the results.

4.2 Study objective to be addressed in this chapter

- To determine if opioid analgesic prescribing trends are affected by socioeconomic deprivation status

4.3 Background

As described in Section 1.10, Wales has a history of poverty, exceeding that of other countries in the UK (Barnard 2018), even considering differences in how socioeconomic deprivation are calculated (Section 1.10). Whilst it is often acknowledged that higher levels of opioid use will be associated with deprivation (Taylor et al. 2019), no study has previously examined the data for Wales specifically. Other UK-focussed studies have described differences in opioid prescribing in areas with markers of socioeconomic deprivation. Notably, Todd et al. (2018) described a ‘pain divide’ between the north and south in England after

scrutinising data from the Health Survey for England (HSE) (Todd et al. 2018). Similar percentages of people reported having high intensity pain but, more people in the north (12.3%) stated being moderately or severely limited by it, compared to 9.2% in the south. Added to this, 2.5% of people in the north of England used opioids compared to 1.7% in the south (Todd et al. 2018). The north-south divide used by Todd et al. (2018) could be deemed arbitrary, in terms of determining socioeconomic deprivation. It perhaps draws on social stereotypes, when in fact different levels of deprivation are seen in all communities.

The results presented in this chapter will use a validated socioeconomic deprivation measure (Welsh Index of Multiple Deprivation, WIMD), as they are reliable and more easily comparable with data from other countries (Section 4.4.1). Jani et al. (2020) examined opioid prescribing data between 2006 and 2017 although deprivation data were not presented as trends (Jani et al. 2020). Higher opioid prescribing rates have been consistently demonstrated in the most socioeconomically deprived areas (Chen et al. 2019; Macfarlane et al. 2020; Torrance et al. 2020). The TOPAS study differs from other published studies by examining changes in prescribing rates, stratified by deprivation quintile, over time. To further build the picture of prescribing across Wales, trends in prescribing rates by opioid-type (weak or strong) and gender, which as previously discussed (Sections 3.5.2 and Section 3.5.3) are associated with different changes in prescribing (Chapter 3), are examined in the context of deprivation. This is a novel aspect of the TOPAS study that has not been found in other studies from the UK.

4.4 Methods

4.4.1 Welsh Index of Multiple Deprivation

The Welsh Index of Multiple Deprivation (WIMD) is the official measure used by the Welsh Government to determine relative deprivation of areas within Wales (Welsh Government 2011). For the TOPAS study, the 2011 Index was used (Welsh Government 2011) and presented in quintiles. It is notable that

deprivation is multifactorial (Table 4.1) and the WIMD does not represent multi-level deprivation e.g. scores are not linear so areas in group 2 are not twice as deprived as those in group 4 (Welsh Government 2011).

Table 4.1: Components of the Welsh Index of Multiple Deprivation (WIMD) (Welsh Government 2011)

Component	Percentage of WIMD Score %
Income	23.5
Employment	23.5
Health	14
Education	14
Geographical access to services	10
Community safety	5
Physical environment	5
Housing	5

The most populated areas of Wales, concentrated in the South of the country, have been shown to have the highest overall levels of deprivation. These areas are principally within the areas of Aneurin Bevan Local Health Board (ABLHB), Cardiff and Vale University Health Board (CVUHB), Cwm Taff Local Health Board (CTLHB) and Abertawe Bro Morgannwg University Health Board (ABMUHB) although areas of substantial deprivation are found in every Health Board (Figure 4.1).

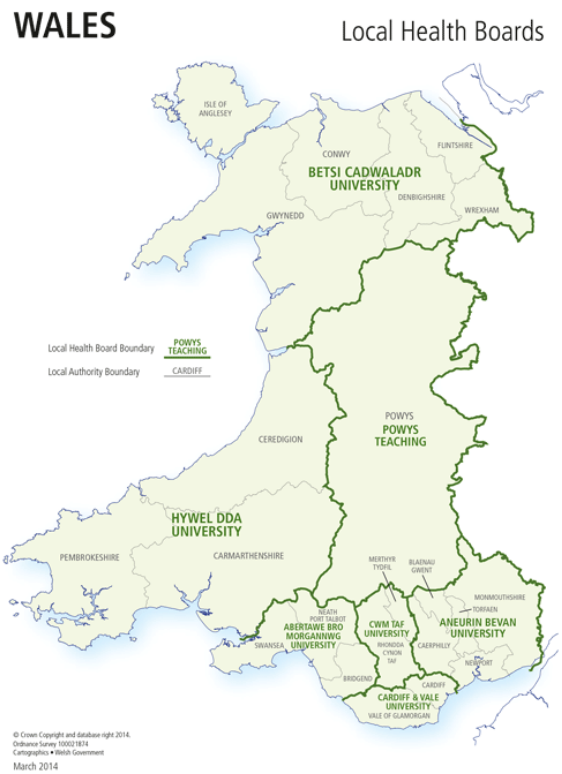


Figure 4.1: Map showing boundaries of Welsh Health Boards in 2014. These boundaries remained in place until March 2019
(Patient Knows Best 2014)

4.4.2 Identification of socio-economic deprivation areas

Lower super output areas (LSOA) are geographic units used in the Welsh Index of Multiple Deprivation (WIMD) calculations. Each LSOA has a population of around 1500 people, although this does vary slightly as the areas have remained unchanged since their inception in 2004 (StatsWales 2019). There were 1896 LSOAs defined across Wales in 2011. The most deprived LSOA in Wales is ranked 1 and calculated using the 8 categories defined by the Welsh Index of Multiple Deprivation (Table 4.1).

Local super output area (LSOA) data was also accessed from StatsWales. The data was presented by LSOA and WIMD quintile and then manually stratified into Health Board areas based on the LSOA, using LSOA mapping from (StatsWales 2010). This data was used to determine the percentage population of each Health Board living in each WIMD quintile area. Those proportions were used to calculate SAIL populations for each quintile, per Health Board, per year from 2005 to 2015. Those population estimates were used to calculate results by 1000 population per relevant area.

4.4.3 Calculation of WIMD populations

The LSOA and corresponding WIMD2011 quintile listed for each person was linked from the Welsh Demographic Service dataset (WDSD) (Appendix C) and added to the main study data set, subsequently extracted to analysis. This allowed data to be stratify by WIMD2011 quintile and had the potential to stratify by LSOA if required.

Welsh population data for people aged 18 years and older for each LSOA, within each Welsh county was available from StatsWales (StatsWales 2021) Population data for 2011 was downloaded and sorted by LSOA, numbers 1 to 1896 where LSOA1 is considered the most socio-economically deprived and LSOA1896 the least deprived. Each LSOA was further organised into WIMD2011 quintiles, where WIMD1, the most socioeconomically deprived included 380 LSOAs and the remaining 4 had 379. The percentage of total Welsh population (2011) located

within each quintile was used to calculate SAIL databank quintile populations. The percentages were assumed to be the same for each year within the study and so used to adjust SAIL databank population 2005 to 2015, then used to adjust per 1,000 population (Appendix C).

Each LSOA population was also matched to the Health Board in which it was located, building up population numbers in WIMD quintiles. Once the WIMD quintile population for each of the seven Welsh health boards was calculated, the percentage of total Health Board population accounted for by each WIMD quintile was computed. The percentages were used to adjust the SAIL populations for each Health Board, thus providing estimates of WIMD2011 quintile population at national and Health Board level for the whole study period (Appendix C).

4.4.4 Missing data

The extracted data contained 785,056 (3.4% of the 11-year total) prescriptions for 144,993 (3.8% of the total) people between 2005 and 2015, where an LSOA or WIMD quintile were not allocated. These data were left out of analyses. SAIL was unable to explain why individuals were not allocated but it could include temporary residents receiving prescriptions whilst on holiday from outside of Wales for example. There are also people registered with Welsh GPs but who have an English address, due to proximity to the Wales-England border. Owing to the large number of data included in the study, it was not considered problematic for the overall analysis that they were not included.

4.4.5 Data extraction and analysis

Individual subjects were identified and their anonymised, linked data for opioid prescriptions and demographics extracted from the SAIL databank as described in Section 2.6. Annual number of prescriptions issued were totalled, stratified by WIMD2011 quintile and further adjusted to W quintile populations (Section 4.4.3). Descriptive statistics described the trends using the full data set from 2005 to 2015. Percentage change over time and Spearman's rank correlations

(Section 2.7.1) were used to examine changes in prescribing rates over the 11-year study period.

Data were stratified into groups based on gender (Section 2.6.5.1) and the opioid type prescribed per prescription (Section 2.6.3). Comparisons between WIMD2011 quintiles used Kruskal-Wallis tests, with Dunn's pairwise comparison and Bonferroni corrections used to confirm statistically significant differences (Section 2.7.3). Comparisons of the number of prescriptions or prescribing rate, between genders within the same quintiles were made using Mann-Whitney U tests (Section 2.7.2).

4.4.6 Log-linear regression

In this study, log-linear regression models were developed to examine factors which may be associated with prescribing rates. Log-linear regression is used to examine the associations between more than two categorical variables. In this study, variables including gender, deprivation quintile, weak or strong opioid and Health Board were transformed into categorical variables to assist the analysis. For example, socioeconomic deprivation quintile 1 (WIMD1) was recoded as 1 and all others 0, or strong opioids coded as 1 and weak opioids as 0.

4.5 Results

4.5.1.1 All opioids

In total, 6,493,712 opioid prescriptions were issued in the most deprived areas compared to 2,752,198 issued in the least deprived over the period examined (2.4 times more). Twenty-nine and a half percent of all opioid prescriptions (n=22,001,509) were issued within the most deprived areas of Wales (29.0% when adjusted to population). The least deprived areas (WIMD5) had 12.5% of all opioid prescribing across the study period (12.2% when adjusted to

population). The distribution of prescribing across the different areas of deprivation remained consistent for the 11-year period examined (Figure 4.2).

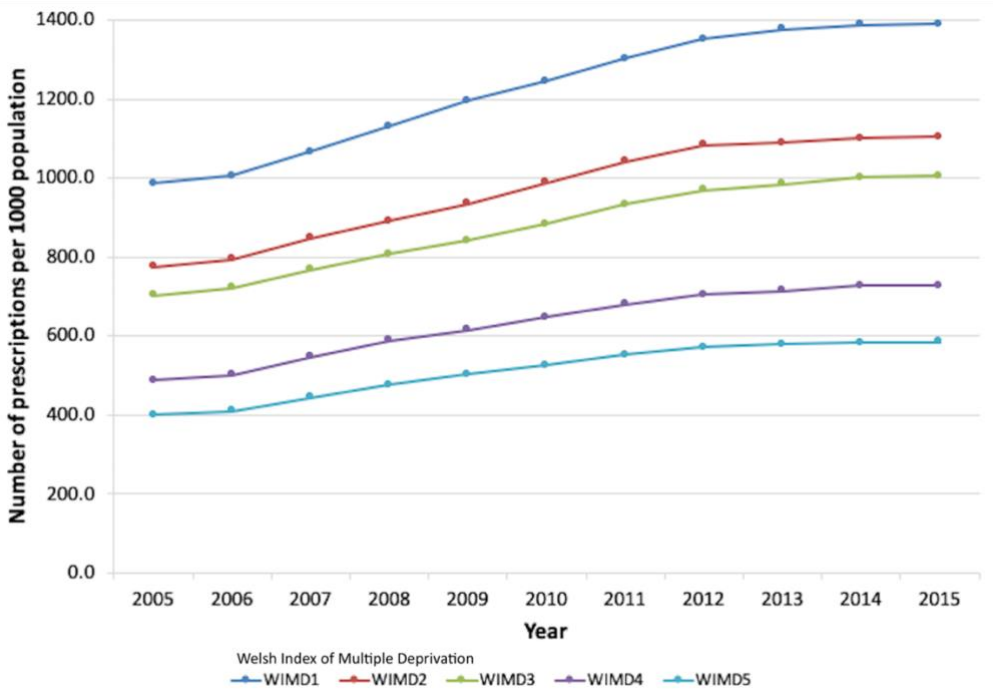


Figure 4.2: Trends in the number of all opioid prescriptions issued by deprivation area and adjusted to the population of each quintile of deprivation in Wales
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived

When examined as a whole, statistically significant differences between the numbers of opioid prescriptions being issued in the 5 areas of deprivation across Wales were detected (Kruskal-Wallis, $p<.001$, $\eta^2=0.839$, $d_{Cohen}=4.569$). Post-hoc analysis confirmed that significantly more prescriptions were issued in the three most deprived quintiles when compared to the least deprived (WIMD1 $p<.001$, WIMD2 $p<.001$ and WIMD3 $p=0.008$) (Appendix C). Significantly more prescriptions were also issued in WIMD1 ($p<.001$) and WIMD2 ($p<0.05$) areas compared to in the WIMD4 quintile. No statistical differences in prescription numbers were detected between quintiles WIMD3 to 5 (Appendix C). Similar outcomes were noted for Kruskal-Wallis analysis of prescribing rate data (Appendix C).

Table 4.2: Comparison of quintile-population adjusted numbers of prescriptions for all opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015.

	Prescriptions per 1,000 population				
	WIMD1	**WIMD2**	**WIMD3**	**WIMD4**	**WIMD5**

2005	987.1	774.8	702.4	487.0	399.7
2015	1389.8	1104.8	1005.2	727.0	585.1
Change rate (%) 2005 - 2015	40.8	42.6	43.1	49.3	46.4
Spearman's r *p-value	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	0.991 p<.001*	>.999 p<.001*

WIMD1 = most socioeconomically deprived, WIMD5 = least socio-economically deprived *p<0.05 = statistically significant

The greatest increase in annual prescription rates were seen in the least deprived areas. WIMD4 areas had an increase of 49.3% and there was a 46.4% increase in WIMD5 (Table 4.2). There was strong correlation between prescribing rates and time for all quintiles over the study. There were fairly large annual increases in the number of prescriptions and corresponding prescribing rates issued in all quintiles in the first seven years of the study period. From 2012 onwards however, those increases became smaller and the trend appeared likely to start reversing beyond 2015.

4.5.1.2 Weak opioids

Over the 11 years examined, 2.4 times more weak opioid prescriptions were issued in the most deprived areas (WIMD1) of Wales compared to the least deprived area (WIMD5) (Table 4.3). For the whole study period, prescribing rates were inversely related to level of deprivation.

Table 4.3: Comparison of quintile-population adjusted numbers of prescriptions for weak opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015.

	Number of prescriptions per 1,000 population				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	937.1	730.5	659.1	455.4	377.2
2015	1166.2	928.9	834.8	605.3	496.8
Change rate (%) 2005 - 2015	24.5	27.2	26.6	32.9	31.7
Spearman's r *p-value	0.882 p<.001*	0.873 p<.001*	0.936 p<.001*	0.945 p<.001*	0.909 p<.001*

WIMD1 = most socioeconomically deprived, WIMD5 = least socioeconomically deprived *p-value <0.05 = statistically significant. Full annual data Appendix C

Statistically significant differences in the number of weak opioid prescriptions issued between each deprivation quintile were identified (Kruskal-Wallis, p<.001, η^2=0.886, d_{Cohen}=5.568). As with the overall trend analysis, significantly more prescriptions were issued in the three most deprived quintiles when compared

to the least deprived (Appendix C). Significantly more prescriptions were issued in WIMD1 and WIMD2 quintiles, when compared to WIMD4. No statistically significant difference was detected between the three higher quintiles however, in terms of total number of prescriptions issued between 2005 -2015 (Appendix C).

As with overall opioid prescribing previously described, the larger increases in the numbers of prescriptions issued each year, were seen in the less deprived areas (WIMD4 and WIMD5) (Table 4.3). There were very strong Spearman's correlations between prescribing rate and time in all quintiles (Table 4.3). The annual number of weak opioid prescriptions peaked in two areas (WIMD2 and WIMD5) in 2012 and as with the number of people (Appendix C), prescribing in all areas started to slow and reduce in the subsequent three years (**Error! Reference source not found.Error! Reference source not found.**). The least deprived quintile demonstrated the smallest reductions in annual prescribing rate between 2013 and 2015, thus drawing prescribing rates within those areas closer to the quintile above.

4.5.1.3 Strong opioids

Over the study period, 2.3 times more strong opioid prescriptions were issued in the most deprived areas of Wales compared to the least deprived area (Figure 4.3). Rate of prescribing and the number of strong opioid prescriptions issued

was inversely associated with deprivation quintile.

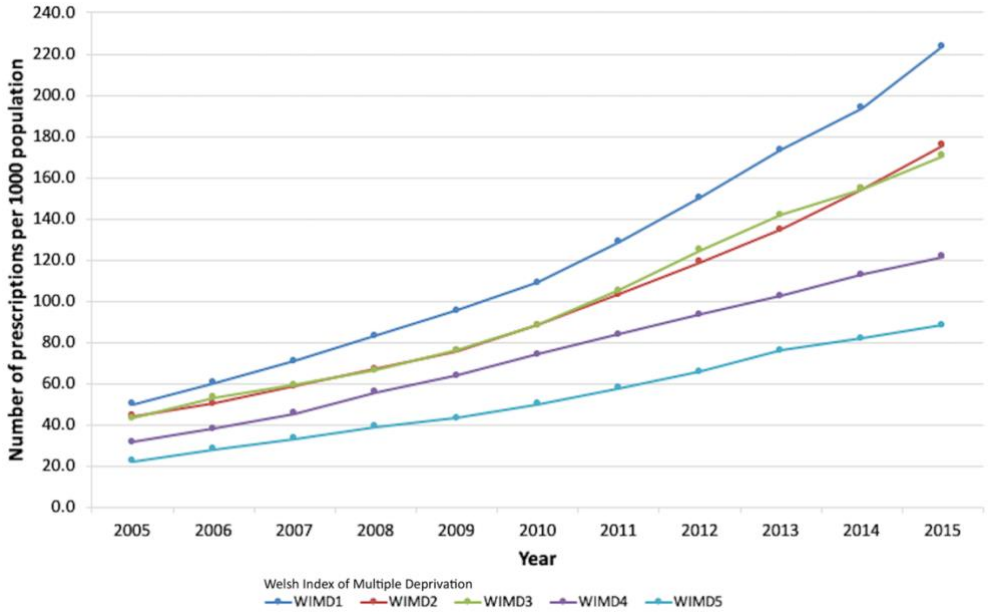


Figure 4.3: Trends in the number of strong opioid prescriptions issued by deprivation area and adjusted to the population of each quintile of deprivation in Wales
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived

The most deprived areas also experienced the largest increase in the number of strong opioid prescriptions (Table 4.4). The smallest increase was seen in WIMD4 areas although those areas still had nearly 4 times increase in the annual number of prescriptions (285.2%, from 31.6 to 121.6 prescriptions per 1,000 population).

Table 4.4: Comparison of quintile-population adjusted numbers of prescriptions for strong opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015.

	Prescriptions per 1,000 population				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	50.0	44.3	43.3	31.6	22.5
2015	223.6	175.9	170.4	121.6	88.3
Change rate (%) 2005 - 2015	346.8	297.1	293.9	285.2	291.9
Spearman's r	>.999	>.999	>.999	>.999	>.999
***p-value**	p<.001*	p<.001*	p<.001*	p<.001*	p<.001*

WIMD1 = most socioeconomically deprived, WIMD5 = least socioeconomically deprived *p-value <0.05 = statistically significant. Full annual data Appendix C

The difference in the number of prescriptions issued within each deprivation quintile across Wales were noted as statistically significant (p=.007, η^2=0.2, d_{Cohen}=1.001), as determined by a Kruskal-Wallis test. However, post-hoc analysis confirmed a statistically significant difference (p<0.01) in the prescribing rate for strong opioids only between the most deprived (WIMD1) and least deprived (WIMD5 areas) (Appendix C).

As the study period progressed, the overall rate of increase in annual prescribing remained consistently higher in the most deprived quintile when rates in the two least deprived quintiles began to level out (Figure 4.3). This resulted in divergence in the number of strong opioid prescriptions being issued in the most deprived areas of Wales, compared to those in the more socioeconomically advantaged areas (Figure 4.3).

Unlike overall opioid prescribing and weak opioid prescribing, there was no clear pattern in the rates of change for strong opioid analgesics. Unlike weak opioid prescribing, a peak in annual prescribing numbers had not been reached within the 11 years of data this study analysed.

4.5.2 Gender differences

4.5.2.1 All opioids

Women received more prescriptions for all types of opioids, regardless of the socio-economic deprivation quintile they lived in (Figure 4.4). The number of prescriptions issued to women in the two least deprived areas (WIMD4 and WIMD5) demonstrated a similar trend to that observed in men living in middle quintiles (WIMD2 and WIMD3) (Figure 4.4).

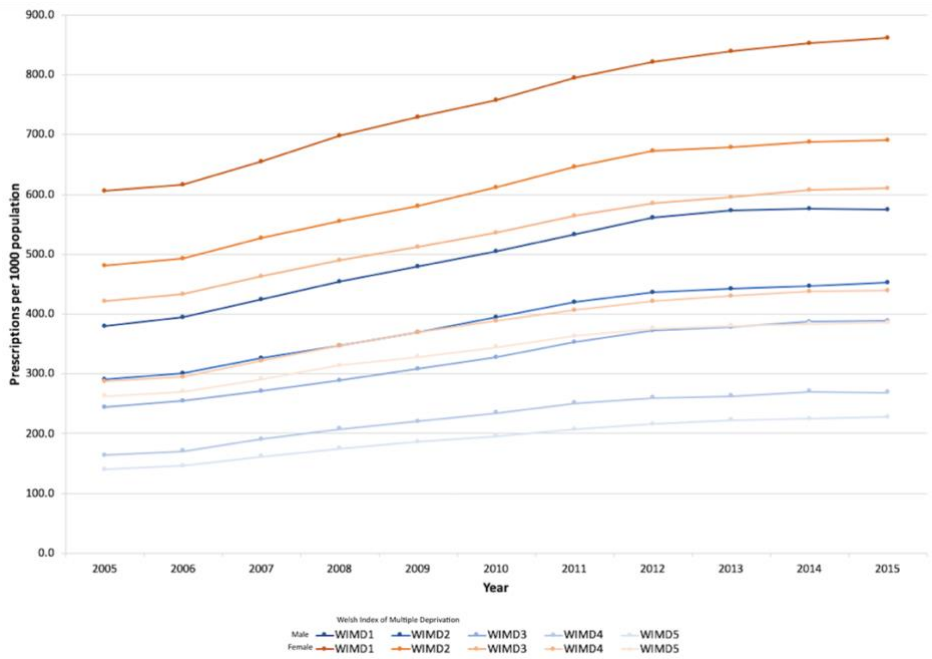


Figure 4.4: Trends in the number of all opioid prescriptions issued to men and women by deprivation quintile and adjusted to quintile-population in Wales
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived

Totaled over the 11 years examined, women received between 51% (WIMD1) and 76% (WIMD5) more opioid prescriptions per 1,000 quintile-population, than men (Table 4.5) which was statistically significant ($p<.001$, $\eta^2=0.717$, $d_{Cohen}=3.817$). The annual percentage increases in the number of prescriptions issued however, were higher for men than women in every quintile (Table 4.5).

Table 4.5: Comparison of quintile-population adjusted numbers of prescriptions for all opioid medicines by Welsh Index of Multiple Deprivation quintiles and gender across Wales between 2005 and 2015

	Number of prescriptions per 1,000 population									
	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2005	380.5	606.6	290.4	480.5	244.0	421.2	163.7	287.0	140.3	262.7
2015	575.1	861.5	452.4	690.0	388.4	610.1	268.6	439.9	227.4	385.3
Change rate (%) 2005 - 2015	51.1	42.0	55.8	43.6	59.2	44.9	64.1	53.3	62.1	46.7
Spearman's r, p-value	0.973 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	0.991 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*
Mann-Whitney (between genders in same quintile)	p<.001*, $\eta^2=0.717$ $d_{Cohen}=3.187$		p<.001*, $\eta^2=0.717$ $d_{Cohen}=3.187$		p<.001*, $\eta^2=0.717$ $d_{Cohen}=3.187$		p<.001*, $\eta^2=0.717$ $d_{Cohen}=3.187$		p<.001*, $\eta^2=0.717$ $d_{Cohen}=3.187$	

WIMD1 = most socioeconomically deprived, WIMD5 = least socio-economically deprived *p<0.05 = statistically significant

Within gender groups, statistically significant differences were observed in the number of prescriptions issued in each quintile (Table 4.5). Between women, significantly more prescriptions were issued in quintiles with greatest deprivation compared to the least (Kruskal-Wallis, $p<.001$, $\eta^2=0.844$, $d_{Cohen}=4.653$). Post-hoc analysis confirmed the number of prescriptions issued in adjacent quintiles (e.g., WIMD1 and WIMD2, WIMD4 and WIMD5) were not statistically different (Appendix C). Neither was there a statistically different number of prescriptions issued in WIMD1 and WIMD3 quintiles ($p=0.128$) (Appendix C).

Comparison of the number of prescriptions issued to men in the five deprivation quintiles demonstrated the same differences as observed for women. Overall, the total number of prescriptions issued to men, per quintile between 2005 and 2015 were significantly different (Kruskal-Wallis, $p<.001$, $\eta^2=0.833$, $d_{Cohen}=4.472$). Adjacent quintiles did not have confirmed statistical differences in number of prescriptions issued (Appendix C) and similarly, WIMD1 and WIMD3 areas were statistically similar in the number of prescriptions issued ($p=0.084$).

Trends in total opioid prescribing demonstrated a slowing in annual percentage increases as the study period drew to its end (Figure 4.5). Interestingly, increases in prescribing were inverse to deprivation, despite the number of prescriptions issued being so much higher in more deprived areas.

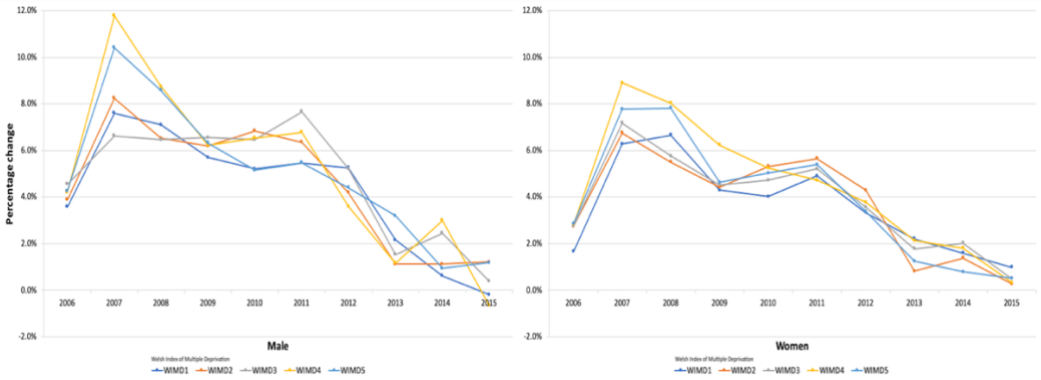


Figure 4.5: Annual percentage change in the number of prescriptions for all opioids by each quintile of deprivation in Wales and gender
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived

4.5.2.2 Weak opioids

Similar trends in weak opioid prescribing were observed in men and women in each deprivation quintile over the study period (Figure 4.6). For both genders, large differences were noted between the most and least deprived quintiles especially. In total, 2.3 times the number of prescriptions per 1,000 population were issued to women living in the most deprived areas (WIMD1) compared to those in the least deprived (WIMD5) (Table 4.6).

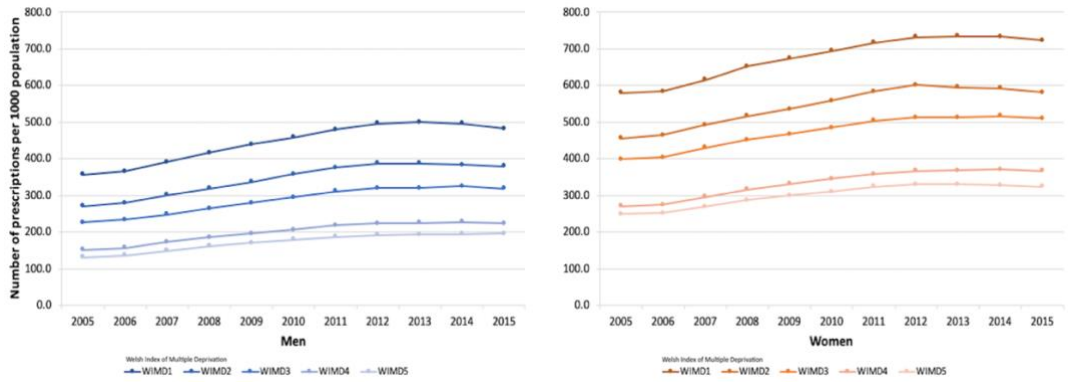


Figure 4.6: Trends in the number of weak opioid prescriptions issued to men and women by deprivation quintile and adjusted to quintile-population in Wales
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived

Table 4.6: Comparison of quintile-population adjusted numbers of prescriptions for weak opioid medicines by Welsh Index of Multiple Deprivation quintiles and gender across Wales between 2005 and 2015

	Number of prescriptions per 1,000 population									
	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2005	357.0	580.1	270.6	456.2	225.9	398.2	151.2	270.3	131.3	249.0
2015	482.9	722.5	379.7	580.9	319.2	510.0	223.3	366.6	196.1	324.1
Change rate (%) 2005 - 2015	35.3	24.6	40.3	27.3	41.3	28.1	47.7	35.6	49.4	30.2
Spearman's r, p-value	0.882 p<.001*	0.873 p<.001*	0.873 p<.001*	0.873 p<.001*	0.936 p<.001*	0.936 p<.001*	0.945 p<.001*	0.945 p<.001*	>.999 p<.001*	0.873 p<.001*
Mann-Whitney (between genders in same quintile)	p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187	

WIMD1 = most socioeconomically deprived, WIMD5 = least socioeconomically deprived *p<0.05 = statistically significant. Annual data in Appendix C

The overall rate of prescribing was less in men than women in every quintile although increases in prescribing were greater (Table 4.6). However, the percentage difference between each quintile was greater than observed between women. Men in the most deprived areas (WIMD1) received 2.6 times more weak opioid prescriptions than those in the least deprived (WIMD5) (Table 4.6).

Rates of weak opioid prescribing began to reduce from 2013 for both genders, resulting in the differences between quintiles beginning to narrow slightly at the end of the study period. Overall prescribing rates for women were significantly higher than for men in equivalent socio-economic quintiles (Figure *4.6*).

Differences in the number of prescriptions issued to women in the five deprivation quintiles, were statistically significant (Kruskal-Wallis, $p<.001$, $\eta^2=0.895$, $d_{Cohen}=5.824$). Post-hoc analysis confirmed significantly more prescriptions were issued in quintiles WIMD1-3 compared to the least deprived quintile (WIMD5) (Appendix C). This was also true for the two most deprived quintiles compared to WIMD4 areas and it also confirmed significantly more prescriptions were issued in the most deprived quintile (WIMD1) compared to the areas of middle deprivation levels (WIMD3).

Fewer differences in the number of prescriptions issued in the different quintiles were observed in men, although the overall comparison was statistically significant (Kruskal-Wallis, $p<.001$, $\eta^2=0.878$, $d_{Cohen}=5.358$). Significantly more weak opioid prescriptions were confirmed to have been issued in the three most deprived quintiles (WIMD1 to WIMD3) when directly compared to the least deprived areas. Post-hoc analysis also confirmed statistically more prescriptions were issued in the two most deprived quintiles (WIMD1 and WIMD2) when directly compared to the 4th quintile (WIMD4) (Appendix C).

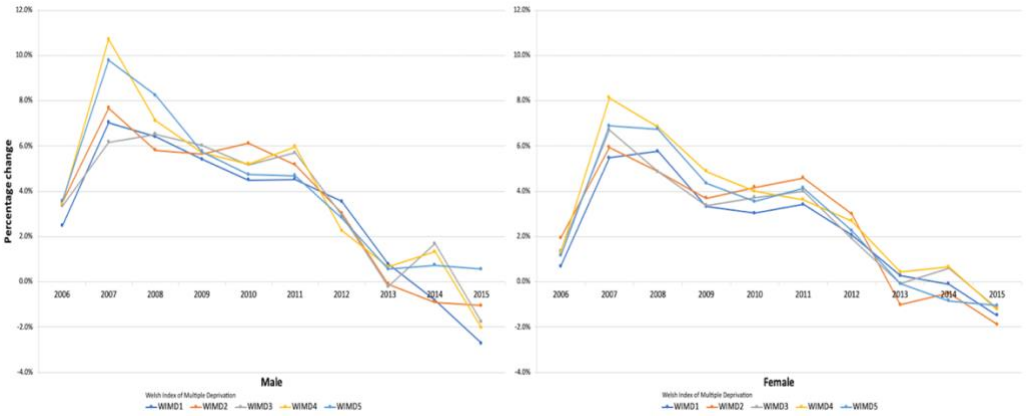


Figure 4.7: Annual percentage change in the number of prescriptions for weak opioids by each quintile of deprivation in Wales and gender
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprive)

The rate of increase in weak opioid prescribing slowed consistently in all quintiles and both genders over the 11 years examined (Figure 4.7). Reductions in prescriptions per 1,000 population were noted in all deprivation quintiles for women by 2015 and all but the least deprived areas for men (Figure 4.7).

4.5.2.3 Strong opioids

Women in each socio-economic deprivation quintile, received more prescriptions for strong opioid medicines, than men in the same areas. The greatest increase in prescribing rate was noted in the WIMD1 quintile (Table 4.7). Increases in prescribing rate were greater for women than men, in every quintile. Despite the empirical differences, strong opioid prescribing rates over the 11 years analysed were only statistically different in the least deprived quintile (WIMD5) (Table 4.7). Spearman's r tests demonstrated strong correlation in all quintiles for both genders, between time and prescribing rate, confirming the upward trends observed between 2005 and 2015 (Table 4.7).

Table 4.7: Comparison of quintile-population adjusted numbers of prescriptions for strong opioid medicines by Welsh Index of Multiple Deprivation quintiles and gender across Wales between 2005 and 2015.

	Number of prescriptions per 1,000 population									
	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2005	23.5	26.5	19.8	24.3	18.0	22.9	12.5	16.7	9.0	13.7
2015	92.2	138.9	72.7	109.2	69.1	100.2	45.3	73.3	31.3	61.2
Change rate (%) 2005 - 2015	292.0	423.7	267.5	349.5	283.3	336.7	262.0	338.3	246.6	346.9
Spearman's r, p-value	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*	>.999 p<.001*
Mann-Whitney (between genders in same quintile)	p=.193, η^2=0.082 d_{Cohen}=0.599		p=.116, η^2=0.118 d_{Cohen}=0.73		p=.101, η^2=0.127 d_{Cohen}=0.764		p=.056, η^2=0.165 d_{Cohen}=0.889		p<.01*, η^2=0.298 d_{Cohen}=1.303	

WIMD1 = most socioeconomically deprived, WIMD5 = least socio-economically deprived. *p<0.05 = statistically significant. Annual data in Appendix C

Comparing prescribing rates between quintiles and by gender, differences were deemed statistically significant for women (Kruskal-Wallis, $p<0.05$, $\eta^2=0.113$, $d_{Cohen}=0.715$) and men (Kruskal-Wallis, $p<0.01$, $\eta^2=0.323$, $d_{Cohen}=1.383$). Pairwise comparisons of strong opioid prescribing rates for women in the different quintiles only confirmed a statically significant difference between the most (WIMD1) and least (WIMD5) quintiles however ($p<0.05$) (Appendix C).

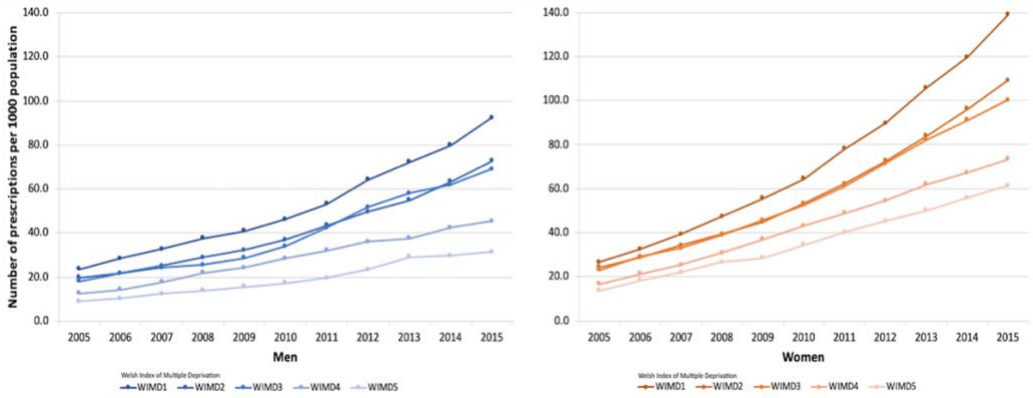


Figure 4.8: Trends in the number of strong opioid prescriptions issued to men and women by deprivation quintile and adjusted to quintile-population in Wales
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived

A slightly different observation was noted in men. Pairwise comparisons between number of prescriptions per 1,000 population issued 2005 -2015, confirmed statistically different rates between the 3 most deprived areas (WIMD1, WIMD2 and WIMD3) and the least deprived (WIMD5). No other differences were observed in prescribing rates between the other quintiles (Appendix C).

As with strong opioid prescribing in general, there was no pattern in terms of the annual percentage increases noted in any of the five quintiles or either gender. Both lower quintiles (WIMD1 and WIMD2) had consistent percentage increases each year (Figure 4.8). In quintiles WIMD3 to WIMD5, there appeared to be greater fluctuation in annual percentage change for men than women (Figure 4.9). Whilst slowing in the rate of increase in prescribing was observed in both genders towards the end of the study, strong opioid prescribing was still rising, with the highest rates in the most deprived areas (Figure 4.9).

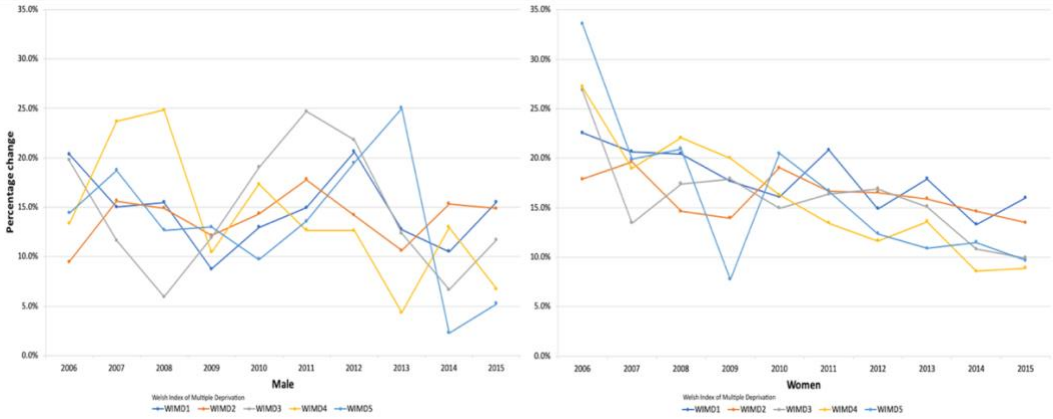


Figure 4.9: Annual percentage change in the number of prescriptions for strong opioids by each quintile of deprivation in Wales and gender
WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived

4.5.3 Log-linear regression outcomes

The log-linear regression results were used to examine which variables might predict the likelihood of receiving a prescription for a strong opioid analgesic. The variables used in the model were deprivation quintile, gender, age and Health Board in the Primary Care medical record. X^2 (8) = 7947.33, p<0.001. The model explained 2% (Nagelkerke R^2) of the variance in strong opioid prescribing and correctly classified 89.4% of cases. The $ß_0$ (constant) for the equation was 4.272, SE=.006, p<.001.

Based on the regression output, people living in the Abertawe Bro Morgannwg, Cwm Taf and Aneurin Bevan University Heath Board areas were more likely and to receive a strong opioid prescription as individuals living in Powys Teaching Health Board (Table 4.8). Living in areas considered to be within the two most deprived quintiles slightly increased the chance of receiving a strong opioid prescription compared to those living in the least deprived. Living in quintiles WIMD3 and WIMD4 however, reduced the likelihood compared to being in WIMD5. Being male reduced the likelihood of receiving a strong opioid prescription, compared to being female. Every year of additional age over the age of 18 years led to an increased likelihood of receiving a strong opioid prescription. So, the receipt of a strong opioid prescription appeared to correlate with increasing age.

Table 4.8: Output from log-linear regression to determine variables which may increase the likelihood of receiving a strong opioid analgesic prescription

Variable	$ß_n$ (SE), p-value*
Deprivation quintile	
WIMD1	1.023 (.002), <0.001
WIMD2	1.045 (.003), p<.001
WIMD3	.980(.003), p<.001
WIMD4	.931 (.003), p<.001
Gender (male)	.952 (.001), p<.001
Age (per year over 18 years)	1.012 (.000), p<.001
Health Board	
Betsi Cadwaladr	.751 (.005), p<.001
Hywel Dda	.696 (.005), p<.001
Abertawe Bro Morgannwg	1.378 (.005), p<.001
Cardiff and Vale	.792 (.005), p<.001
Cwm Taf	1.225 (.006), p<.001
Aneurin Bevan	1.055 (.005), p<.001

*p-value <.05 = statistically significant

This model was a poor predictor for strong opioid prescribing, which was likely to be due to all included data being initially selected by the presence of an opioid prescription (Chapter 2).

4.6 Discussion

4.6.1 Summary and reflection on findings

Nearly a third of all opioid prescriptions were issued to people living in the most deprived areas of Wales. Whilst this might have led to an assumption that prescribing would have increased more in the most deprived areas, compared to the least, it was not the case. In fact, overall opioid prescribing rates rose more in less deprived areas over the study period. With the possibility of a reduction in overall prescribing, it appears levels of prescribing might draw closer between quintiles. However, strong opioid prescribing rates were shown to be increasing more rapidly in the most deprived quintiles. Different to weak opioid prescribing, there were signs of increasing disparity between strong opioid exposure in areas of greatest and least deprivation across Wales. The log-linear regression reported here was not an effective means of predicting which of those variables might be most important. Future analysis should include data for people not receiving opioid analgesic prescriptions, to increase the model accuracy.

It was already known from previous results that women received more prescriptions of weak and strong opioids than men (Chapter 3). Women in every quintile had increases in strong opioid prescribing that were much larger than those observed in their male counterparts. Overall, prescribing rates were highest for women living in the most socioeconomically deprived areas of Wales. Of interest was the largest gender difference in prescribing rate, noted in the least deprived quintile (WIMD5). However, as with overall prescribing, there was increasing separation of strong opioid prescribing rates between the quintiles of socio-economic deprivation for men and women as the study period drew to an end. In simple terms, there is evidence that the gap between the poorest and richest in Welsh society is widening.

4.6.2 Contextualising results with existing literature

The findings presented here are consistent with those from the rest of the UK which demonstrate opioid prescribing increases with deprivation (Todd et al. 2018; Macfarlane et al. 2020; Chen et al. 2019; Curtis et al. 2019; Torrance et al. 2018; Schifanella et al. 2020). The Welsh data revealed 2.4 times more prescriptions were issued to people living in the most socioeconomically deprived areas compared to those in more affluent areas. Most UK studies have highlighted correlates between deprivation quintile and opioid prescribing, but not reflected on trends in areas with differing socioeconomic scores. Schifanella et al. (2020) reported spatial association between rates of opioid prescribing and markers of deprivation such as unemployment, low educational attainment and poor housing. Their findings, whilst not reported as a trend analysis, were consistent between 2015 and 2018 and used LSOA level data rather than multiple deprivation quintiles (Schifanella et al. 2020). It revealed that particular geographical areas could be demonstrated to have significant changes in prescribing in that period. However, using LSOA spatial models showed that often, significant differences were only noted in relatively discrete units of area e.g., 40 out of 186 LSOAs in Sandwell, West Midlands, accounted for the average increase of 70mg OMEQ observed during the study period (Schifanella et al.

2020). Practices in the most deprived areas of England were found to be more likely to prescribe all opioids and particularly high dose opioids (greater than 120mg oral morphine equivalent dose per day) (Curtis et al. 2019). Again, small reductions have been noted in overall opioid prescribing in England since the mid-2000s (Curtis et al. 2019; Taylor et al. 2019), as in Wales. High dose opioid prescribing was examined for this study and the results are presented in Appendix D.

TOPAS data confirms those observed in Scotland between 1995 and 2010, where increases in prescribing was noted and more so in areas with of greater socio-economic deprivation (Ruscitto et al. 2015). Whilst strong opioid prescribing correlated with deprivation, percentage increases by quintile were not provided. However, as in this study, there was a small reduction in weak opioid prescribing and a significant increase in strong opioid prescribing by study end (Ruscitto et al. 2015). More recently, a larger study from Scotland calculated that people in the most deprived areas were 3 to 4 times more likely to receive weak and strong opioid prescriptions, respectively (Torrance et al. 2018). In this study, these figures were 1.7 and 1.8 times respectively, so almost half the difference noted in Scotland. The data in Scotland was complete for all prescriptions dispensed, whereas TOPAS data was more selective, based on prescriptions issued to 78% of the population (Chapter 2). However, the shape of the trends noted were similar between Wales and Scotland over a similar time period (Torrance et al. 2018). Deprivation is calculated differently in Scotland, compared to Wales (Table 1.1). Given Wales is classified as the most deprived country in the UK, it could be the differences between most and least deprived are not as great as elsewhere. What impact this has on prescribing is not clear, however.

This study observed a south-north divide, prescribing increased with deprivation, with the most deprived areas predominantly in the south of the country. A north-south divide has been used to explain patterns of English opioid prescribing, with northern England commonly defined as the North East, North West and Yorkshire and Humber regions (Todd et al. 2018). Regional variation

has also been examined using geographical latitude as the measure of north or south (Mordecai et al. 2018). Others have reported on north-south variation in prescribing without clearly defining where the dividing line lies (Chen et al. 2019). Whilst geography cannot account for deprivation alone, it is known that there is more widespread socioeconomic deprivation in the north of England, compared to the south (Crisp et al. 2009; Joseph Rowntree Foundation 2017). Todd et al. (2018) observed demographic factors of people reporting chronic pain, such as age, gender and anxiety levels, appeared similar between those in the north and south. However, larger differences were noted in income levels (42.8% of people in the north compared to 32.4% in the south in the lower 2 quintiles), self-reported health status ('bad' or 'very bad' reported by 7.6% of subjects in the north compared to 5.5% in the south) (Todd et al. 2018). Prescribers in the north of England have been observed to issue more opioid prescriptions than their southern counterparts (Todd et al. 2018; Mordecai et al. 2018; Curtis et al. 2019; Chen et al. 2019).

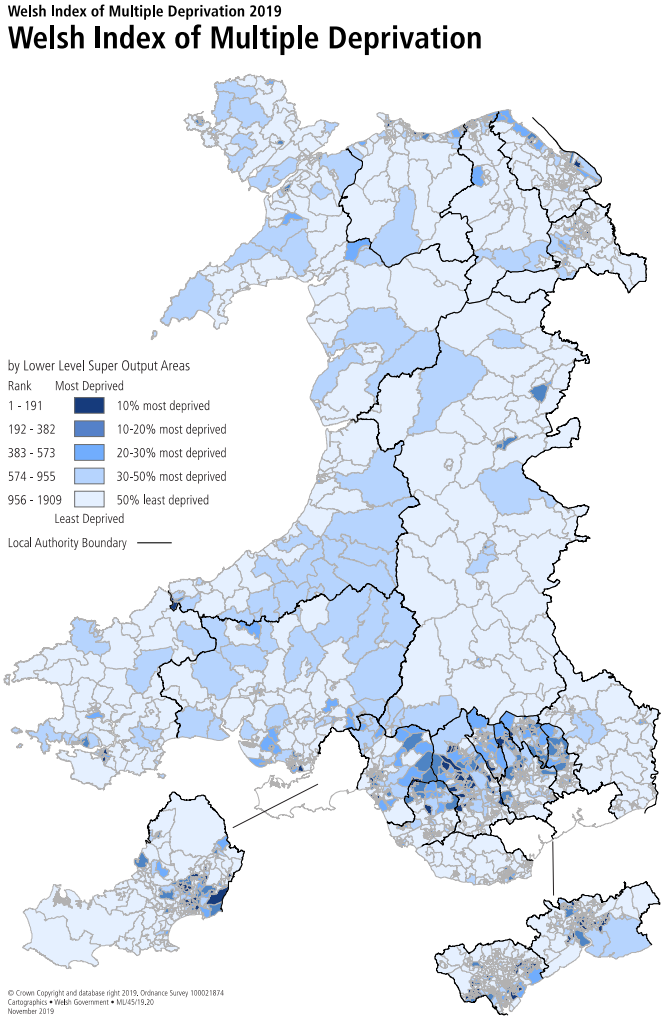


Figure 4.10: Welsh Index of Multiple Deprivation 2019
(StatsWales 2019)

Using oral morphine equivalence, a higher burden of weak and strong opioids was more commonly issued in the north (Mordecai et al. 2018; Curtis et al. 2019). A study examining data from a small geographic area of Leeds and Bradford, in the north of England, reported a greater likelihood of opioid prescribing with increased levels of deprivation. This was within an area that would be generally classed as 'deprived' relative to areas in the south of the country (Foy et al. 2016). Schifanella et al. (2020) confirmed that examining data at LSOA level, differences within areas that fall into the same index of multiple deprivation quintile, can be determined (Schifanella et al. 2020). This perhaps suggests that broad categories of deprivation or geographical areas, used in WIMD and others, are insufficient on their own to explain the patterns of

prescribing noted. For example, Schifanella et al. (2020) describes an area of the West Midlands that as whole had a notable increase in opioid prescribing between 2016-2018. When analysed at LSOA level, the increase was accounted for by just over 20% of the total area's population. Whilst the LSOAs contributing to that area were grouped together in one part of the district, they were a small but exceptional part of a larger whole (Schifanella et al. 2020). Further analysis of opioid prescribing by LSOAs in Wales would be beneficial to allow more precise targeting of local communities for interventions to address it. In all likelihood a combination of broad and focused analysis would be helpful over time to examine changes in prescribing and monitor variation across the country.

Although not examined in this study, opioid prescribing has been correlated with greater perceived pain intensity or pain reporting in the UK (Toye et al. 2017; Todd et al. 2018; Torrance et al. 2018; Macfarlane et al. 2020; Jani et al. 2020). A prevalence of 36.7% in the north of England and 35% in the south has been reported. Pain was moderately or severely limiting for 12.3% of respondents in the north and 9.2% in the south (Todd et al. 2018). Pain prevalence in the general UK population have been estimated at up to 44% (Fayaz et al. 2016). No measure was available in Wales at the time of this study that could be used as a direct comparator. The Welsh Health Survey in 2015, however described 15% of people being limited by health problems or disability which may suggest a similar prevalence of moderate to severe pain. Self-reported pain in multiple sites has also shown correlation with opioid use. An adjusted risk ratio of 16.66 (CI 15.42 – 17.99) was noted for people from all over the UK, reporting pain in seven or more sites, compared to those without any sites of pain although receiving opioids (Macfarlane et al. 2020). High-dose opioid prescribing has also been shown to be more prevalent in primary care practices with greater numbers of patients on long-term condition registers (Curtis et al. 2019). Interestingly, pain intensity was not demonstrated to be significantly different between groups of people taking 99-199mg and more than 200mg oral morphine equivalent daily dose in a large Australian study. Socio-economic status did inversely correlate with dose however (Campbell, Nielsen, Bruno, et al. 2015). Pain intensity was

also not found to be predictive for opioid prescribing in a predominantly rural, deprived cohort in the USA (Kapoor & Thorn 2014).

Higher levels of opioid prescribing in areas of greater socioeconomic deprivation is a consistent finding around the world (McDonald et al. 2012; Smith et al. 2019; Bosetti et al. 2019; Islam & Wollersheim 2019). The American 'opioid crisis' is probably the most documented pattern of prescribing worldwide (Weisberg and Stannard 2013; McGreal 2018; Stoicea et al. 2019; Wen and Sadeghi 2020). Between 2006 and 2012, the prescribing rate increased from 72.4 to 81.3 prescriptions per 1,000 people nationwide (Centers for Disease Control and Prevention 2021) but particularly in areas associated with higher levels of unemployment and deprivation (Weisberg et al. 2014; McGreal 2018; Stoicea et al. 2019). More recently, there is evidence that prescribing of opioids is reducing across north America (Kurani et al. 2020). Overall rates have dropped significantly from 81.3 prescriptions per 100 people in 2012 to 46.7 prescriptions per 100 people in 2019 (Centers for Disease Control and Prevention 2021). The finding of a closing gap between the most and least deprived areas has been observed in America. The percentage reduction in opioid prescriptions issued, was inversely related to deprivation quintile (Kurani et al. 2020). However, some of the most deprived counties continue to have much higher rates, for example Tift County in Georgia had an opioid prescribing rate of 178 prescriptions per 100 people in 2019 (Centers for Disease Control and Prevention 2021). Reports from Australia have illustrated higher levels of opioid prescribing in more rural and less affluent areas (Degenhardt et al. 2015; Islam & Wollersheim 2019). Islam and Wollersheim (2019) demonstrated between 2013 and 2016, adjusted odd ratio (AOR) for opioid prescribing was 1.59 (95% CI 1.48 – 1.71) in the most deprived areas compared to an AOR of 1 for the least deprived areas of Australia (Islam and Wollersheim 2019). Rates of opioid prescribing also vary widely across European. Between 2014 and 2016, opioid consumption in Germany was observed to average 21,346 defined daily doses (DDDs) per 1,000,000 inhabitants, compared to 66 DDDs/1,000,000 inhabitants in Ukraine (Bosetti et al. 2019).

Whilst opioid prescribing rates vary across developed countries, higher rates of prescribing in poorer areas are a consistent feature. Is deprivation a satisfactory reason for prescribing larger quantities of opioid analgesics, however? Whilst pain prevalence may be higher in more deprived areas, evidence would not support the widespread use opioids to address it. Reducing inequality would likely reduce the variation seen in the health of people with different socioeconomic status, given the links between deprivation and pain. Lessening inequity requires political solutions and a genuine commitment to improve social mobility and working conditions (Marmot 2017). Such aspirations are often cited and in Wales, they form the basis of Government policy (Welsh Government 2019). However, it takes time and whilst efforts to reduce inequality continue, measures still need to be put in place to address prescribing as a means of harm reduction.

4.6.3 Gender differences and deprivation

It is known women receive more prescriptions for opioid analgesics than men in the UK and worldwide, where opioids are commonly prescribed (Campbell et al. 2015; Bedson et al. 2016; Mazure and Fiellin 2018; Todd et al. 2018; Torrance et al. 2018; Taylor et al. 2019). Data presented here, confirmed this and that there were additional associations between gender and deprivation.

Bedson et al. (2016) examined trends in the incidence of opioid initiation, for musculoskeletal pain between 2002 – 2013. Whilst it was shown women had a higher incidence than men, for opioid initiation every year, the rate of increase was higher overall for men (Bedson et al. 2016). Unlike results shared here, data was not stratified by deprivation and statistical significance of the differences was not provided. However, assuming rate of initiation and overall rates of prescribing are linked, the all-opioid trend findings in this study are consistent with those of Bedson et al. (2016), in that women had higher rates of prescribing, but lower rates of increase than men (Bedson et al. 2016). The reason for the observation cannot be elucidated from this study and warrants further research. Closing the gender gap in prescribing could be considered a sign of improving

healthcare equity. However, if it resulted in high levels of opioid prescribing in men and women, would it necessarily be a success or, given what is known about the harms of opioids, actually a sign of failure?

Svendsen et al. (2014) observed Norwegian women in the lowest income quartile and who were either unemployed or in receipt of disability pensions, were more likely to receive persistent opioid prescriptions than women with higher incomes or who were employed. The study did not explore whether unemployment or receipt of financial support was the cause or result of living with pain. It is an issue worthy of further research. Women in all categories were more likely than men to receive long-term opioids, although the difference between odds ratio increasing as income also increased. Whilst this part of the study did not analyse prescribing persistence, that the largest gender differences in prescribing rates were in the least deprived quintiles, was supported by Svendsen's work (Svendsen et al. 2014).

Higher pain prevalence and reported intensity have been frequently cited to be higher in females than males (Todd et al. 2018; Mazure & Fiellin 2018). Todd et al.'s. study of pain intensity and opioid utilisation, observed statistically significant increases in reporting of severe and moderately limiting pain in females, compared to males (Todd et al. 2018). A prescribing trend analysis did not form part of that study, however. The Scottish Family Health Study includes questions on pain experience. From that, 71.8% of people reporting severe pain were female, although women were over-represented in the study (63.7% of respondents) (Torrance et al. 2018). Whilst trend analysis stratified by gender or deprivation, has not been reported in Scotland, a point prevalence study from 2012 confirmed significantly higher ($p<.001$) rates of weak opioid prescribing for women, than men which TOPAS findings were consistent with (Torrance et al. 2018). As with data presented here, there was not a statistically significant difference in strong opioid prescribing rates between men and women (Torrance et al. 2018), although it was not stratified by deprivation quintile, so direct comparison was not possible.

Of concern from this work was the trajectory of increase of strong opioid prescribing rate (Figure 4.8) for women in the most deprived quintile, which does not appear to have previously been reported. Overall, opioid prescribing rates in Wales since the end of the study period in 2015 have levelled, with some initial signs of reduction (Shared Services Partnership 2021). However, the rate of strong opioid prescribing was continuing to increase at the end of the study period. The difference in pain experience of men and women has recently been highlighted in mainstream media with particular focus on gynaecological conditions such as endometriosis and complications of vaginal mesh surgery (Barnett 2020; Connolly 2020; Marsh 2021; Warraich 2021). Women have described feeling disbelieved in respect of the pain they are reporting and consequently, often 'fobbed off' with painkillers, which are frequently opioids, as a consequence (Connolly 2020; Marsh 2021). It perhaps suggests the lack of understanding of female-specific conditions and ingrained gender constructs could be as influential on prescribing decisions as the presenting symptoms (Marsh 2021). Further research is clearly needed in terms of gender-differences in pain experience and its management.

Mazure and Fiellin (2018) commented on the impact gender difference in the context of the north American opioid crisis (Mazure & Fiellin 2018). They highlighted women were more likely than men to access opioids on prescription than illicitly and for pain, which is supported by other studies including in Wales (Cicero et al. 2009; Holloway et al. 2018; Fischer et al. 2018). Although women are currently less likely to present with opioid use disorder (NWIS - Information Services 2019), there is evidence they develop problematic use more quickly than their male counterparts (Hernandez-Avila et al. 2004; McHugh et al. 2018). Substance misuse is also more common in areas of greater socioeconomic deprivation (Liddell 2019; Taylor et al. 2019). Adverse effects of opioids have been shown to differ between men and women (Fillingim et al. 2009; National Academies of Sciences, Engineering, and Medicine 2017), although it cannot be stated with certainty that women experience worse effects. The combination of rising strong opioid use in women living under the most challenging conditions is

suggestive the prevalence of any resulting harm could be disproportionate and further widen health inequalities.

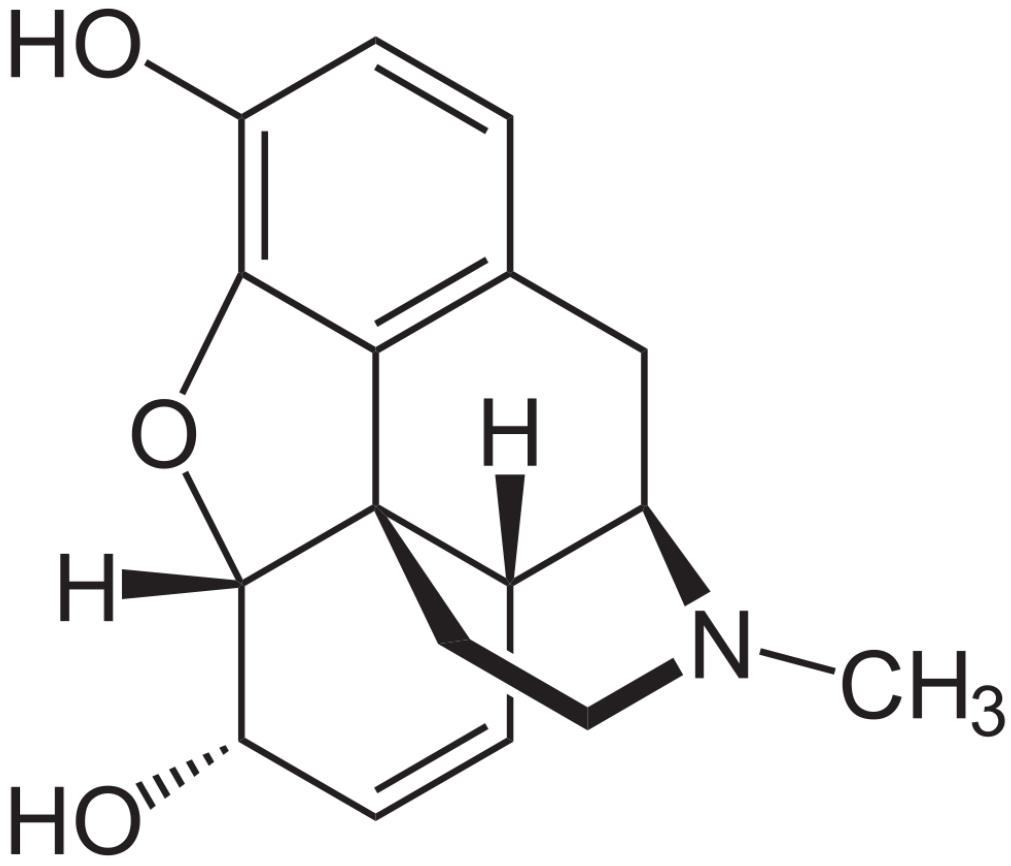
4.7 Conclusion

Opioid prescribing is significantly more common in areas with higher levels of socioeconomic deprivation. This is one of few studies which has examined opioid prescribing trends by deprivation. Whilst other studies have demonstrated large increases in opioid prescribing, this study goes further by showing how trends vary depending on deprivation and gender.

A high burden of opioid prescribing within deprived and unhealthy populations should be a cause of great concern for healthcare leaders and policymakers. The long-term harm of opioids is likely to be felt more severely in areas where levels of health and general well-being are already poor. An additional apprehension is the potential for prescribed opioids to be diverted or used in conjunction with illicit substances, as in Wales, areas of high prescribing are also those with high levels of substance misuse. Access to services is problematic, in no small part due to the geography of the country. This research has demonstrated however, prescribing is a nationwide concern and whilst certain areas have larger populations of concern, no area is devoid of problematic opioid use.

There is an urgent need to address the reasons that pain prevalence and opioid prescribing are so much higher in the populations specified in this study. Examining the motivation of prescribers and those receiving prescriptions is necessary to develop new strategies which target the most vulnerable people, in a manner that considers the complexities of their pain and the lives that they are leading.

Chapter 5
Prescribing trends in oral morphine equivalent dose



"No man ever sank under the burden of the day. It is when tomorrow's burden is added to the burden of today that the weight is more than a man can bear."
George MacDonald

Chapter 5 – Prescribing trends in oral morphine equivalent dose

5.1 Chapter overview

A review of non-cancer pain and the use of opioids in its management, as well as the use of large datasets was laid out in Chapter 1. The second chapter set out the methods used for the main analyses involved in Phase 1 of this research. The results so far have illustrated significant increases in all opioid prescribing and of strong opioids in particular. Women were more likely to receive opioid prescriptions than men. People aged 45 years and above have higher rates of prescribing than those who are younger. Opioid prescribing was much higher in areas of greatest socioeconomic deprivation and again, women appear disproportionately affected. This chapter scrutinises the data in a different way. Using a purpose-designed measure to determine oral morphine equivalent dosing changes, trends will be examined whilst also looking at which drugs were prescribed. Comparisons will also be made with the trends in prescription numbers to determine if it is a more effective method for determining 'opioid burden'.

5.2 Study objective to be addressed in this chapter

- To analyse trends in oral morphine equivalent doses and prescribing duration using estimated measures for each

5.3 Background

The internationally recognised daily defined dose (DDD) used by the World Health Organisation (WHO) is often used as the measure of burden in studies and data reviews in practice. The WHO define DDDs as '*the assumed average maintenance dose per day for a drug used for its main indication in adults*' (WHO Collaborating Centre for Drug Statistics Methodology 2021). To decide DDDs for any drug, WHO classifies medicines according to the organ or body system they act upon, as well as their pharmacological properties. The number of DDDs is used as an expression of consumption (Figure 5.1**Error! Reference source not**

found.). Whilst this system is defined and accepted internationally, it is not necessarily reflective of the indications or recommended doses in any particular country. This is pertinent for opioids, where there is considerable inequality of access worldwide (Richards et al. 2020).

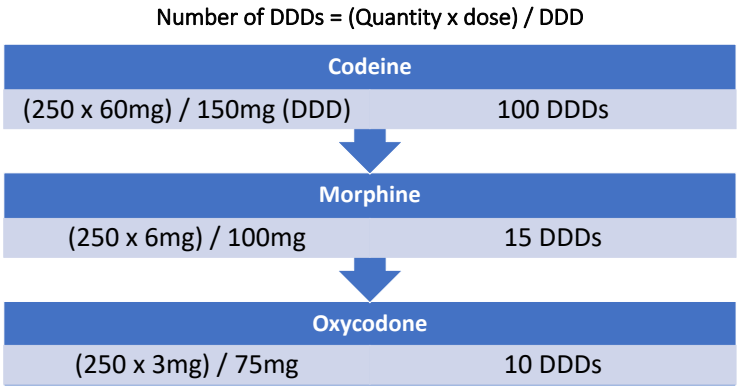


Figure 5.1: Comparing Defined Daily Dose (DDD) to Oral Morphine Equivalent dose (OMEQ). Doses of codeine, morphine and oxycodone are equianalgesic
(WHO Collaborating Centre for Drug Statistics Methodology 2021)

As DDDs are different for different drugs and for different formulations of the same drug, it does not allow easy comparison or perhaps, can foster the impression that the 'burden' of some drugs is less than it might be (Svendsen et al. 2011). Average daily quantity (ADQ) was developed in the UK by an expert group, using 'English' dosing as the basis, purportedly to reflect clinical practice more accurately (Walley and Roberts 2000). However, ADQs are not devised for all medicines, including newer opioids such as tapentadol, which does not have DDD measures listed. Consequently, neither DDDs nor ADQs can be used to consistently measure all opioid prescribing in the UK. Added to that ADQs cannot be used as a comparator to prescribing in other countries around the world.

In recent years, guidelines in countries with widespread use of opioids for chronic, non-cancer pain have included suggested maximum oral morphine equivalent doses of between 90mg and 120mg per day (Faculty of Pain Medicine 2021). To assess prescribing data compliance with guidance would necessitate the conversion of each opioid being used to an equivalent DDD or ADQ measures. In practice, DDDs and ADQs are used for reviewing prescribing data,

rather than for guiding prescribing itself. Perhaps a question arises of how useful it is in guiding prescribers towards better practise.

Recent analyses of UK prescribing data have used OMEQ as a measure of opioid burden (Zin et al. 2014; Mordecai et al. 2018) alongside more conventional measures such as the number of prescriptions. Svendsen and colleagues (2011) have previously suggested OMEQ is a preferable measure to use as a comparator of prescribing between countries and more accurately reflects clinical practice (Svendsen et al. 2011). As with DDDs and ADQs however, OMEQ is not a faultless measure. Challenges exist insofar as gaining agreement on conversions which are unequivocal (Shaw and Fudin 2013; Schatman et al. 2016). However, the arguments around using OMEQ as a measure of prescribing burden, are perhaps conflated with disparate views on equianalgesic dosing in clinical practise (Natusch 2012; Shaw and Fudin 2013; Schatman et al. 2016).

Equianalgesic dosing is generally a clinical action, whereby a prescriber attempts to determine the dose of one opioid which provides the same level of analgesia as a specified dose of another (Natusch 2012). Disparities in how equianalgesic doses are calculated either by individuals (Rennick et al. 2016) or when using purposefully designed ‘calculators’ (Shaw and Fudin 2013) have been demonstrated however.

Some argue morphine equivalence is fundamentally flawed, due to pharmacogenomic differences and small pharmacokinetic differences between individual drugs. Using equianalgesic dosing to determine dose limits is suggested to be problematic as individuals handle medicines differently and dependent on multiple other factors including other illnesses, medicines, renal function and so on (Schatman et al. 2016). However, if an individual requires an opioid medicine but is unable to tolerate their current prescription, prescribers will require some idea of a roughly equivalent dose of an alternative to change them to (Natusch 2012).

Using OMEQ as a measure of prescribing burden, potentially has another purpose. In terms of supporting prescribers to understand data and contextualise it within their practice, it might be helpful (Svendsen et al. 2011). Whilst understanding of equivalence or equianalgesic dosing is generally considered poor (Shaheen et al. 2009; Rennick et al. 2016), it is likely better than for DDDs or ADQs, which are not easily interpreted into common terms. OMEQ might enable prescribers to understand the implications of their prescribing, which would seem an important aspect of enabling change, over time.

Higher opioid burden in socioeconomically deprived areas has started to provoke great concern in health leaders and policy makers alike here in the UK (Taylor et al. 2019). Deprivation is inextricably linked with poorer health outcomes and a higher incidence of chronic pain. Further, higher levels of prescribing of dependency forming medicines, other than opioids, has been observed in areas of greater deprivation (Taylor et al. 2019; Torrance et al. 2020) and confer additional risk of harm to the user.

National and international concerns around opioids have tended to focus on strong analgesics such as morphine and oxycodone (Scherrer et al. 2016; Lin et al. 2017). This is likely due to the agenda being predominated by the USA opioid crisis, where strong opioids and oxycodone especially, are heavily implicated (McGreal 2018). There is evidence though, dose and duration are as likely indicators of harm or potential for dependence as the choice of drug (Gomes et al. 2011; Els et al. 2017). Estimates suggest as many as 78% of people using opioids for extended periods, experience adverse effects (Els et al. 2017).

The results presented here, therefore, examine the trends in opioid prescribing between 2005 and 2015 using an estimated OMEQ (denoted as $OMEQ_e$) and compare them to prescription numbers issued over the same period. The data are stratified by individual drug as a means of assessing if one measure is a better reflection of prescribing burden than the other. As already discussed in this thesis, gender differences in pain perception and opioid prescribing have

been observed (Section 1.8 and Section 3.6.5) and so gender differences in opioid burden were also analysed.

5.4 Method

5.4.1 Data extraction analysis

Identified subjects had their anonymised, linked data for opioid prescriptions and demographics extracted from the SAIL databank as previously described in Section 2.6Chapter 2. The number of prescriptions issued each year were totalled and stratified by drug and further adjusted to SAIL population (Section **Error! Reference source not found.**) for initial reporting. Estimated OMEQ was calculated for each drug product as set out in Sections 5.4.2 to 5.4.5 and then stratified into groups based on gender (Section 2.6.5.1) and also WIMD2011 quintile (Section 4.4.1 to Section 4.4.3). Descriptive statistics described the trends using the data sets created, from 2005 to 2015. Percentage change over time and Spearman's rank correlations (Section 2.7.1) analysed changes in prescribing rates and $OMEQ_e$ for each drug over the 11-year study period. Comparisons between $OMEQ_e$ for each drug and WIMD2011 quintiles used Kruskal-Wallis tests, with Dunn's pairwise comparison and Bonferroni corrections used to confirm statistically significant differences (Section 2.7.3). Comparisons of the prescribing rate and $OMEQ_e$, between genders were made using Mann-Whitney U tests (Section 2.7.2).

5.4.2 Opioid prescriptions

For each prescribing event listed in the main extraction data table, the prescribed opioid product was available from the Primary Care General Practice dataset. Each product was given a 'flag' for the main opioid within it e.g., codeine, morphine, oxycodone etc. Data could be sorted either by the drug group e.g., codeine or by the product prescribed e.g., co-codamol 30/500 (Table 5.1). For the purposes of annual trend analysis, the drug groupings were used. Products were used to determine estimated oral morphine equivalence ($OMEQ_e$).

Table 5.1: Example of calculations for OMEQe (milligrams) using 2005 data for female subjects. Annualised total = oral morphine equivalent of daily dose x annual number of prescriptions. Process repeated for each drug product e.g., buprenorphine 10mcg/hour patch, BuTrans 10mcg/hour patch and totalled for each year

	Units used for calculating annualised $OMEQ_e$			
Drug product	**Recommended daily dose* ****	**Oral morphine equivalent of daily dose (mg)*** ********	**Annual number of prescriptions**	**Annualised total oral morphine equivalent burden (mg)**
Buprenorphine				
10micrograms/hour	1 patch per week	24	28	672
52.5 micrograms/hour	1 patch twice a week	126	354	44,604
Codeine				
Co-codamol 8/500	2 tablets 4 times a day	6.4	17,952	114,893
Codeine phosphate 30mg	2 tablets 4 times a day	24	16,293	391,032
Zapain capsules (30/500)	2 tablets 4 times a day	24	112	2688
Dihydrocodeine				
Co-dydramol 10/500	2 tablets 4 times a day	8	153,047	1,224,376
DHC Continus 90mg MR tablet	1 tablet twice a day	18	1,009	18,612
Remedeine tablet	2 tablets 4 times a day	16	1,295	20,720
Fentanyl				
Durogesic 100mcg/hour patch	1 patch every 3 days	360	131	47,160
Fentanyl 200micrograms SL lozenge	1 lozenge 4 times a day	120	40	4,800
Fentanyl 25mcg/hour patch	1 patch every 3 days	90	3,429	308,610
Morphine				
Morphgesic SR 10mg m/r tablet	1 tablet twice a day	20	73	730
MXL 60mg m/r capsule	I capsule once a day	60	23	1,380
Oramorph 10mg/5mL liquid 100mL	5mL every 2 hours	120	573	68,760
Sevredol 20mg tablet	1 tablet every 6 hours	120	299	35,880
Oxycodone				
Longtec 20mg m/r tablets	1 tablet twice a day	80	1	80
Oxycodone HCl 20mg capsule	1 capsule every 4 hours	240	250	60,000
OxyContin 80mg m/r tablet	I capsule twice a day	320	262	83,840
Tramadol				
Dromadol XL 200mg m/r tablet	1 tablet once daily	20	11	220
Tramadol 50mg capsule	2 capsules 4 times a day	40	93,918	3,756,720
Tramacet 325mg/37.5mg	2 tablets 4 times a day	30	4,450	133,500
Other				
Co-proxamol 32.5mg/325mg tablet	2 tablets 4 times a day	26	82,015	2,132,390
Hydromorphone HCl 1.3mg capsule	1 capsule every 4 hours	58.5	6	351
Pethidine HCl 50mg tablet	1 tablet every 4 hours	30	2,381	71,430

*(BNF: British National Formulary - NICE. 2021) **(Datapharm Ltd 2021) ***(Faculty of Pain Medicine 2021.) ****(Pain Management Centre and Oxford University Hospitals NHS Foundation Trust 2020)

5.4.3 Choice of opioid

Opioid products commonly associated with the treatment of substance misuse – e.g., buprenorphine 2mg and 8mg, Subutex® and Suboxone® branded products and injectable opioids were removed from the main analysis to provide a picture of prescribing of opioids more likely to be for non-cancer related pain.

5.4.4 Estimated oral morphine equivalent dose ($OMEQ_e$)

At the time of this study, the SAIL datasets were not accessing prescription dispensing data. Whilst data for prescriptions filled in community pharmacies is

available from Primary Care Services in Wales (Shared Services Partnership 2021) it was not available for the anonymisation process required by the data linkage used by SAIL (Ford et al. 2009). Without the anonymous linkage process (Section 2.4.2), individuals cannot be followed and consequently, the relationship between a prescription and an event in Primary Care cannot be determined.

SAIL have access to information about the product and strength prescribed e.g., 'Morphine sulphate MR tablets 10mg' which is automatically coded when inputted into General Practice Primary Care (GPPC) notes systems when the prescription is generated during the appointment. However, the dosing instructions. e.g., 'Two tablets to be taken twice daily' and the quantity provided e.g., '56 (fifty-six) tablets' are classed as 'free text entry' and whilst coded within the prescription, are not coded within the GPPC system and consequently, not available to SAIL. Lack of dosing information meant it was not possible to calculate an accurate 'oral morphine equivalent' (OMEQ) dose. Using OMEQ allows improved comparison of opioid burden between different drugs and different products, by putting everything into the same form (Svendsen et al. 2011). Concerns around opioid use are linked to the doses being taken and the duration of use, more so than the individual drug itself.

Oral morphine equivalent dose (OMEQ) is normally calculated by multiplying the dose for each prescription (this can be a combination of doses e.g. 10mg + 30mg tablets to give a total of 40mg per dose), by the equi-analgesic ratio of the opioid in question (Zin et al. 2014). The number of days' supply provided by each prescription is then divided by the numerical daily dose (NDD) which is a figure normally taken from the free text on the prescription (e.g., 'One tablet to be taken twice daily'). This method allows an OMEQ dose to be calculated per prescription or can be calculated per individual over longer periods to, for example, calculate annual OMEQ doses (Zin et al. 2014; Mordecai et al. 2018).

5.4.5 Development of an estimated OMEQ

An estimated OMEQ ($OMEQ_e$) was devised. Injections and buprenorphine products specified for the management of opioid misuse were cleansed from the data-tables. Oral and transdermal opioids in common use were retained for examination. Each product was allocated its OMEQ value based on conversion tables available for clinical practice (Appendix D) (Faculty of Pain Medicine 2021). The $OMEQ_e$ value was based on the opioid dose within the product and then multiplied by the recommended dose per day, as available from the British National Formulary (BNF: British National Formulary - NICE. 2021) or the summary of product characteristics (Datapharm Ltd 2021) (Appendix D**Error! Reference source not found.**). The $OMEQ_e$ for each product was multiplied by the number of prescriptions issued each year to determine annual totals.

Table 5.2: Examples of oral morphine equivalent (OME) dosing tables, used to develop OME-proxy measures for comparing opioid burden for the TOPAS study. The tables below are reproduced from Opioids Aware (April 2020) (Faculty of Pain Medicine 2021)

Oral opioids

	Potency ratio with oral morphine	**Equivalent dose to 10mg oral morphine**
Codeine phosphate	0.1	100mg
Dihydrocodeine	0.1	100mg
Morphine	1	10mg
Oxycodone	2	5mg
Tapentadol	0.4	25mg
Tramadol	0.15	67mg

Transdermal opioids

Buprenorphine patch strength	5 microgram/hr	10 microgram/hr	20 microgram/hr	35 microgram/hr	52 microgram/hr	70 microgram/hr
Oral morphine	12mg	24mg	48mg	84mg	126mg	168mg
Fentanyl patch strength	12 microgram/hr	25 microgram/hr	50 microgram/hr	75 microgram/hr	100 microgram/hr	
Oral morphine	45mg	90mg	180mg	270mg	360mg	

Annual total $OMEQ_e$ (milligrams) for each drug grouping were calculated by adding together all product totals (Appendix D**Error! Reference source not found.**).

5.5 Results

5.5.1 Number of prescriptions

More than half of all opioid prescriptions (53.9% mean average) issued in Wales between 2005 and 2015 were for codeine. In 2015, codeine prescriptions accounted for 54.3% of the total of all opioid prescriptions examined. Prescriptions for codeine increased 54.8% over the study period (Table 5.3).

Table 5.3: Trends in the number of opioid prescriptions per 1,000 population 2005 – 2015, stratified by drug

	Prescriptions per 1,000 population							
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other
2005	8.2	350.9	157.4	6.2	16.9	5.5	95.1	56.6
2015	34.9	543.3	111.1	18.3	104.2	25.7	156.3	6.9
Rate change (%) 2005-2015	323.8	54.8	-29.4	193.3	515.8	371.5	64.4	-87.8
Spearman's r, *p-value	0.991, p<.001*	>.999 p<.001*	<-.999, p<.001*	0.882, p<.001*	>.999, p<.001*	0.964, p<.001*	0.882, p<.001*	-0.724, p<0.05*

p-value <0.05 =statistically significant. Annual data in Appendix D

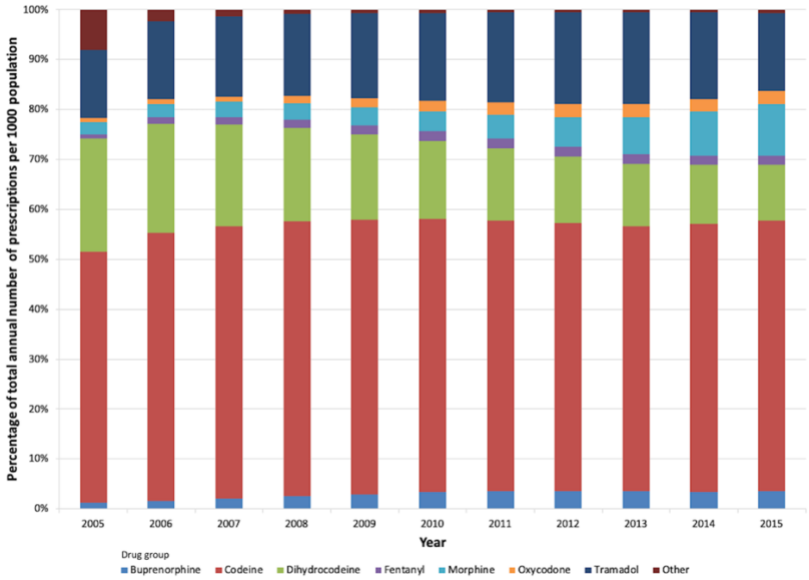


Figure 5.2: Trends in the number of prescriptions of named opioids by percentage of the total number of issued opioid prescriptions

The annual number of morphine prescriptions had the greatest increase of any named drug across the eleven years examined. Prescriptions for morphine increased 515.8% (Table 5.3). Morphine prescriptions accounted for 2.4% of the total opioid prescriptions in 2005, rising to 10.4% by 2015 (Figure 5.2**Error! Reference source not found.**). Spearman's r correlations between prescriptions per 1,000 population and time were strong for all drugs. Dihydrocodeine and 'other' opioids had negative correlations, confirming the reduction in prescribing rate over the study period (Table 5.3). In the 'other category, the reduction was mostly a result of dextropropoxyphene being withdrawn from the UK market in mid-2005 (Appendix D). Comparison of the annual prescribing rates revealed statistically significant differences between the total number of prescriptions per 1,000 population between 2005 and 2015, when compared by drug (Kruskal-Wallis, $p<.001$, $\eta^2= 0.839$. $d_{Cohen}= 4.56$). Pairwise comparisons by drug, confirmed there were significantly more prescriptions for codeine issued than for all but dihydrocodeine and tramadol (Appendix D).

Post-hoc Dunn's pairwise tests, and Bonferroni corrections confirmed codeine prescribing rates were significantly higher for all drugs other than dihydrocodeine, tramadol. Those three drugs did not have statistically significantly different prescribing rates between 2005 and 2015. Dihydrocodeine and tramadol were also confirmed to have statistically higher rates of prescribing than all other drugs apart from morphine (Appendix D). Dihydrocodeine prescriptions decreased by 29.4% (Table 5.3) between 2005 and 2015. Whilst this was the only commonly prescribed opioid that reduced during the study period, it was still the third most frequently prescribed opioid in 2015 (Table 5.3**Error! Reference source not found.**).

Annual numbers of tramadol prescriptions peaked in 2013 (180.9 prescriptions per 1,000 population) (Appendix D**Error! Reference source not found.**) at which point there had been a 90.2% increase from 2005 (95.1 prescriptions per 1,000 population) (Appendix D). Between 2013 and 2015, there was a 13.6% (from 180.9 to 156.3 prescriptions per 1,000 population) reduction in the annual

number of tramadol prescriptions. Oxycodone prescriptions increased by 371.5% over the eleven years examined (Table 5.3**Error! Reference source not found.**). In 2015, oxycodone was the second most frequently prescribed 'strong' opioid although four times as many prescriptions for morphine were issued in the same year (Table 5.3**Error! Reference source not found.**).

Analysis of the medicines included in the 'other' group are included in Appendix D.

5.5.2 Prescribing trends by oral morphine equivalence dose ($OMEQ_e$)

The total annual oral morphine equivalent dose issued in the form of prescriptions examined for this study doubled (from 37,662,651 milligrams to 76,428,768 milligrams per day) over the 11 years observed (Appendix D). This was 94.1% when adjusted to the population (Table 5.4**Error! Reference source not found.**).

Table 5.4: Daily oral morphine equivalent dose (milligrams) issued on prescription, adjusted to 1000 population, stratified by drug

Estimated oral morphine equivalent dose (milligrams) per 1,000 population				
	2005	**2015**	**Rate change (%) 2005 – 2015**	**Spearman's r, p-value***
Buprenorphine	422	1,107	162.2	0.936, p<.001*
Codeine	5,795	10,449	80.3	>.999, p<.001*
Dihydrocodeine	1,996	1,488	-25.4	-0.973, p<.001*
Fentanyl	1,168	2,691	130.4	0.809, p<0.01*
Morphine	1,419	7,081	399.2	>.999, p<.001*
Oxycodone	580	2,554	340.3	0.927, p<.001*
Tramadol	3,395	5,905	73.9	0.882, p<.001*
Other	1,493	291	-80.5	-0.291, p=0.385
Total	16,268	31,568	94.1	

*p-value <0.05 = statistically significant. Annual data Appendix D

Codeine, the most prescribed opioid in Wales, had the highest $OMEQ_e$ per day (Figure 5.3**Error! Reference source not found.**) and the $OMEQ_e$ per 1,000 population increased by just over 80% (Table 5.4). Over the same period, dihydrocodeine, which has equivalent potency to codeine and is often used as the alternative 'weak' opioid, reduced in $OMEQ_e$ per day by 25.4%. Tramadol had an overall increase of 74% over the study period, although the annual total

$OMEQ_e$ started to reduce from 2014 (Appendix D**Error! Reference source not found.**).

The four main 'strong' opioid being prescribed in Wales, (buprenorphine, fentanyl, morphine and oxycodone) were noted to have large increases in $OMEQ_e$ between 2005 and 2015 (**Error! Reference source not found.**Figure 5.3**Error! Reference source not found.**). Morphine daily dose increased by nearly five times over the eleven years examined. By 2015, morphine was being prescribed at around three times the equivalent dose of either oxycodone or fentanyl and just over six times the $OMEQ_e$ of buprenorphine (Table 5.4).

Consequently, in terms of $OMEQ_e$, codeine accounted for 35% of the opioid burden in Wales, tramadol for 22% and morphine for 14%, resulting in 71% of the opioid burden between 2005 and 2015 being due to three drugs (Figure 5.3).

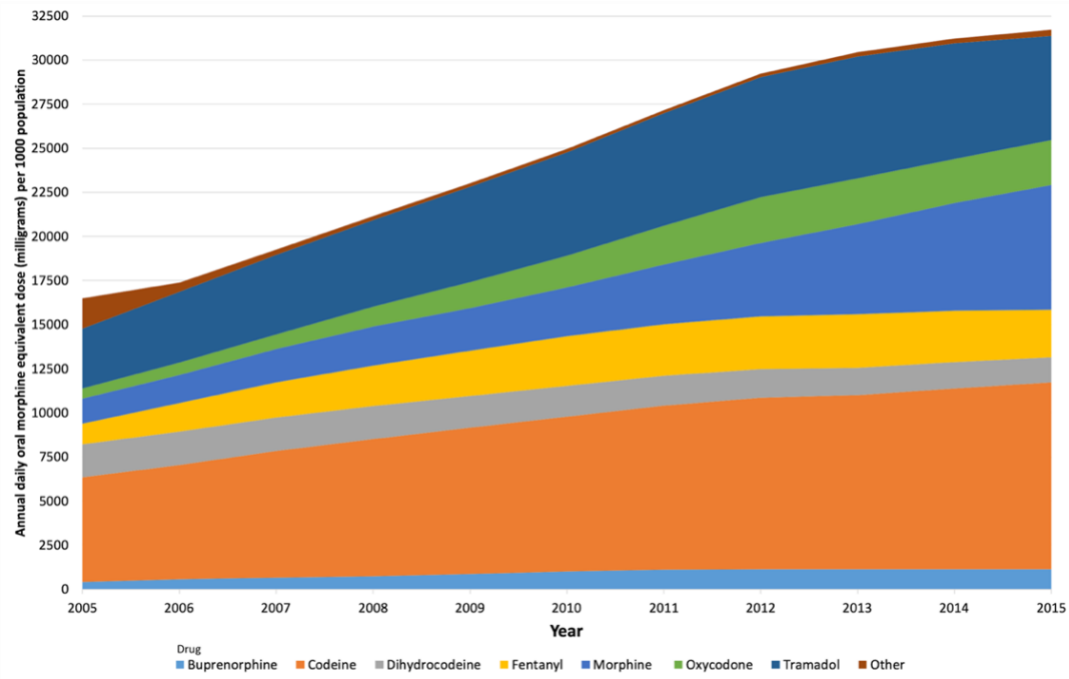


Figure 5.3: Trend in annual total daily oral morphine equivalent dose (milligrams) per 1,000 population, stratified by drug

A significant difference (Kruskal-Wallis, $p<.001$, $\eta^2= 0.837$, $d_{Cohen}= 4.54$) between the total $OMEQ_e$ for each named opioid group listed was found. Pairwise comparisons confirmed codeine $OMEQ_e$ were significantly higher than the $OMEQ_e$ for buprenorphine, dihydrocodeine, oxycodone and 'other' opioid

analgesics but not fentanyl, morphine, or tramadol. The same comparisons were noted for 'other' opioids. Tramadol $OMEQ_e$ was significantly greater than buprenorphine and oxycodone also (Appendix D).

5.5.3 Gender differences in oral morphine equivalent dose ($OMEQ_e$)

Over the study period, women received 53% more in terms of oral morphine equivalence dose than men (388,851,661 milligrams and 254,585,182 milligrams respectively) (Figure 5.4). The difference between the total $OMEQ_e$s was statistically significant (p=.001, η^2= 0.424, d_{Cohen}= 1.72) when examined using a Mann-Whitney test. Both genders demonstrated large increases in the $OMEQ_e$ prescribed (Appendix D), with male $OMEQ_e$ rising by 111.5% (from 14,486,770 to 30,635,826 milligrams, Spearman's r=>.999, p<.001) and female $OMEQ_e$ by 96.5% (from 23,180,854 to 45,557,834 milligrams, Spearman's r=>.999, p<.001).

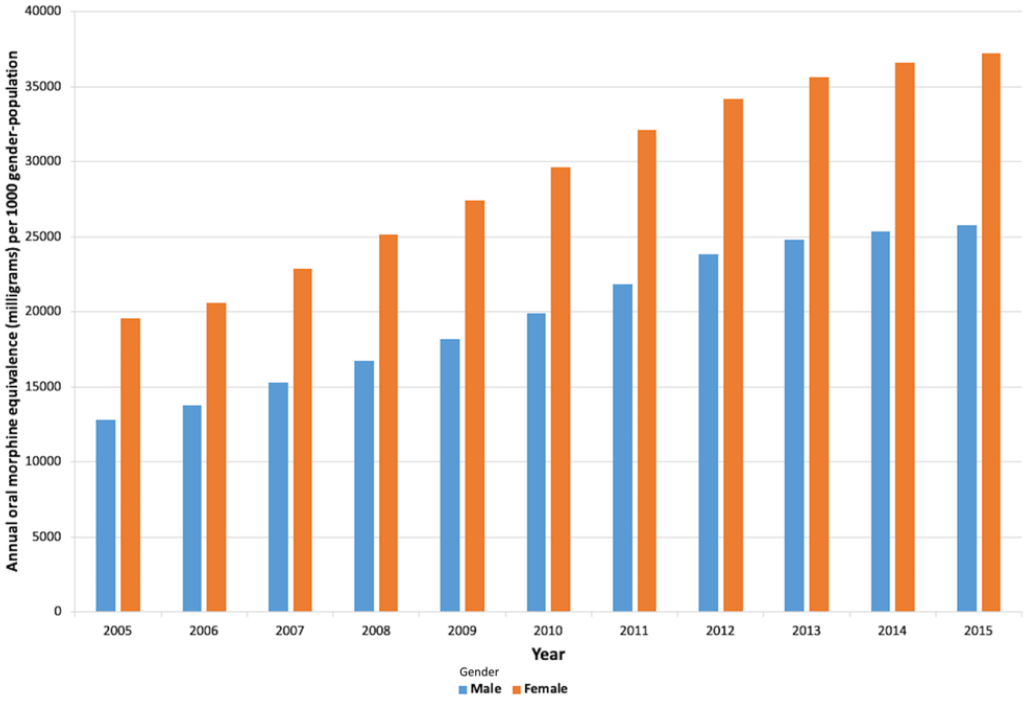


Figure 5.4: Trends in annualised $OMEQ_e$ (milligrams) per 1,000 population stratified by gender

5.5.3.1 Gender differences in $OMEQ_e$ by drug

When examined by drug prescribed, there were statistically significant differences between genders in terms of total annual $OMEQ_e$ prescribed (Table 5.5). There was no statistical difference between the $OMEQ_e$ for morphine and

oxycodone issued to men and women when examined by total milligrams prescribed or by milligrams per 1,000 gender-adjusted population (Table 5.5).

Women had higher percentage changes in $OMEQ_e$ than men for most opioids, except codeine and tramadol (Table 5.5). However, women received overall, total higher $OMEQ_e$ than men for every opioid prescribed, whether examined by total milligrams prescribed (Appendix D) or $OMEQ_e$ per 1,000 population (Table 5.5).

Table 5.5: Trends in Total Annualised Oral Morphine Equivalent Doses (milligrams) per 1,000 population issued by gender. P-values calculated using Mann-Whitney tests for each drug

	Oral morphine equivalent dose (milligrams) per 1,000 population							
Year	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other
Men								
2005	363	4388	1685	761	1327	564	2720	1024
2015	850	8389	1269	1956	5809	2315	4945	253
Rate change (%) 2005 – 2015	134.1	91.2	-24.7	157.1	337.8	310.2	81.8	-75.3
Spearman's r, p-value*	0.936, <.001*	>.999, <.001*	<-.999, <.001*	0.945, <.001*	>.999, <.001*	0.918, <.001*	0.882, <.001*	-0.191, 0.574
Women								
2005	478	7134	2291	1556	1506	595	4037	1939
2015	1356	12447	1700	3405	8315	2787	6837	328
Rate change (%) 2005 – 2015	183.5	74.5	-25.8	118.8	452.2	368.1	69.3	-83.1
Spearman's r, p-value*	0.920, <.001*	>.999, <.001*	<-.999, <.001*	0.773, <0.010*	>.999, <.001*	>.999, <.001*	0.882, <.001*	-0.582, >0.050
Mann-Whitney (Men:Women) p-value*, η^2, d_{Cohen}	<0.050*, 0.291, 1.28	<.001*, 0.561, 2.261	<.001*, 0.717, 3.187	<.001*, 0.540, 2.168	0.332, 0.053, 0.475	0.270, 0.060, 0.505	<0.010* 0.388, 1.593	<0.050*, 0.207, 1.022

*p-value < .05 = statistically significant. Annual data Appendix D

Total fentanyl $OMEQ_e$ per 1,000 population (gender-adjusted) was 91% greater for women than men (35,188 versus 18,435 milligrams per 1,000 population respectively). The difference in the total $OMEQ_e$ of morphine prescribed was not statistically different over the 11 years examined. Although very large percentage increases were seen in both genders, women had 35% more $OMEQ_e$ prescribed than men in that time (44,051 versus 32,556 milligrams per 1,000 gender-adjusted population respectively) (Appendix D). Codeine $OMEQ_e$ per 1,000 population was the highest of all opioids for both genders (Figure 5.5). Women received 53% higher $OMEQ_e$ per 1,000 population than men between 2005 and 2015 (Table 5.5**Error! Reference source not found.**).

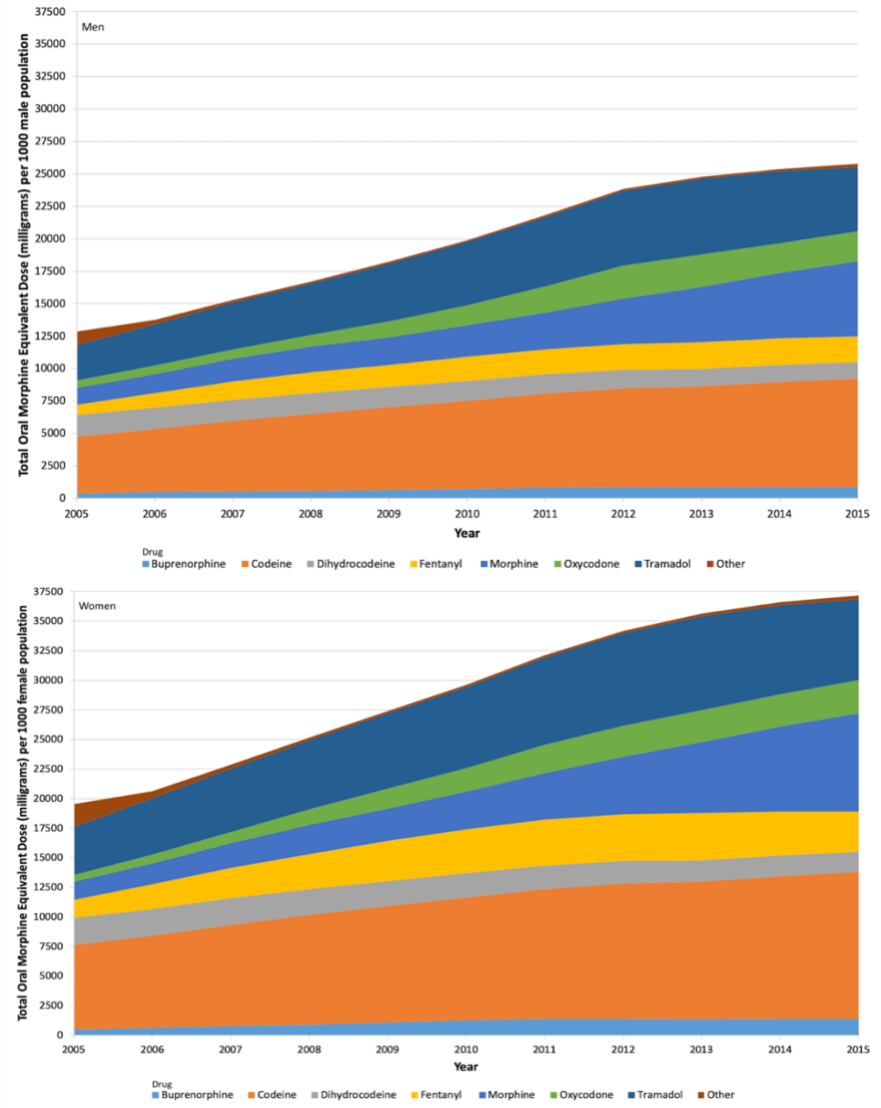


Figure 5.5: Trends in total Oral Morphine Equivalent Dose (milligrams) per 1,000 population, stratified by drug prescribed and examined by gender (Top – men, bottom – women)

Statistically significant differences were noted for the total $OMEQ_e$ of each drug prescribed to men (Kruskal-Wallis, $p<.001$, $\eta^2= 0.827$, $d_{Cohen}= 4.37$). Codeine was the drug for which $OMEQ_e$ prescribed was significantly different to all but morphine and tramadol (Appendix D).

The differences in $OMEQ_e$ per drug prescribed to women, were shown to be statistically significant (Kruskal-Wallis, $p<.001$, $\eta^2= 0.816$, $d_{Cohen}= 4.211$). Post-hoc analysis confirmed a slightly different pattern of variance compared to men (Appendix D). For example, the $OMEQ_e$ of codeine were not confirmed to be statistically different to those of morphine and fentanyl, two strong opioids which are much less frequently prescribed than codeine (Appendix D).

5.5.3.2 Gender differences in $OMEQ_e$ per prescription

The trends in the number of prescriptions issued by gender have been previously discussed (Section 3.5.3). Gender did not determine a statistically significant difference between the average total $OMEQ_e$ per prescription when all prescriptions were examined using a Mann-Whitney test (Appendix D). However, the $OMEQ_e$ per prescription issued was higher for men, for each of the major opioids prescribed (**Error! Reference source not found.**Table 5.6).

Statistically significant differences in the $OMEQ_e$ per prescription by gender were noted using Mann-Whitney tests for buprenorphine, dihydrocodeine, fentanyl, morphine and oxycodone (Table 5.6**Error! Reference source not found.**). Drugs generally considered 'weak' opioids (codeine, dihydrocodeine and tramadol) all demonstrated modest increases in $OMEQ_e$ per prescription for both genders (Table 5.6**Error! Reference source not found.**).

Table 5.6: Trends in oral morphine equivalent dose (milligrams) per prescription issued and by drug, stratified by gender. P-values calculated using Mann-Whitney tests

	Oral morphine equivalent dose (milligrams) per prescription issued								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
Men									
2005	98	17	13	187	89	113	36	27	24
2015	46	20	14	169	71	110	38	60	33
Percentage change (%) 2005-2015	-53.0	14.9	4.7	-9.4	-20.0	-2.8	6.1	124.0	34.3
Spearman's r,	-0.926	0.958	0.671	-0.932	-0.970	0.032	0.858	0.995	0.998
p-value*	<.001*	<.001*	<0.050*	<.001*	<.001*	0.925	<0.010*	<.001*	<.001*
Women									
2005	97	16	12	187	83	102	36	26	23
2015	32	19	13	137	66	93	38	56	31
Percentage change (%) 2005-2015	-67.0	17.2	6.2	-26.8	-19.9	-9.1	5.5	113.2	35.4
Spearman's r,	-0.998	0.963	0.866	<-.999	-0.970	-0.546	0.905	0.991	0.995
p-value*	<.001*	<.001*	<0.010*	<.001*	<.001*	0.082	<.001*	<.001*	<.001*
Mann-Whitney									
p-value*	<0.050*	0.217	<0.050*	<0.010*	<0.050*	<.001*	0.797	0.652	
η^2	0.233	0.071	0.283	0.362	0.194	0.671	0.004	0.01	
d_{Cohen}	1.103	0.552	1.257	1.508	0.983	2.855	0.126	0.197	

*p-value <0.05 = statistically significant. Annual data in Appendix D

Strong opioids all appeared to reduce in $OMEQ_e$ per prescription for both genders (Table 5.6), most notably for buprenorphine where although prescription numbers increased, they were predominantly for low $OMEQ_e$ products (Figure 5.6**Error! Reference source not found.** and Appendix D). The 'other' category of drugs was the drug category with the greatest $OMEQ_e$ increase over the study period (Figure 5.6**Error! Reference source not found.** and Figure 5.7). An initial reduction in $OMEQ_e$ per prescription in this group was due to removal of low $OMEQ_e$ co-proxamol (dextropropoxyphene) from the UK market in 2005, following safety concerns. The rise seen towards the end of the study period is attributed to the introduction of tapentadol, a drug which has a high oral morphine equivalence. It is notable that since 2011, when the drug was released in the UK, $OMEQ_e$ per prescription for 'other' opioid analgesics began to increase quite rapidly for both genders (Figure 5.6 and Figure 5.7**Error! Reference source not found.**).

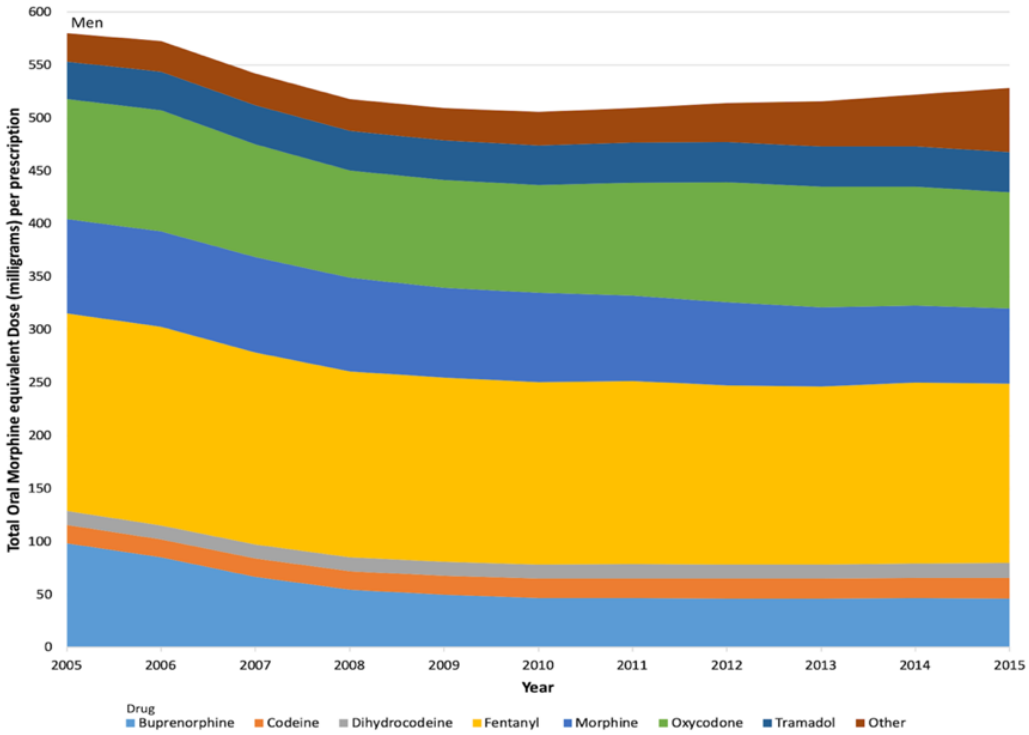


Figure 5.6: Trends in Oral Morphine Equivalent Dose (milligrams) per prescription issued to men and stratified by drug

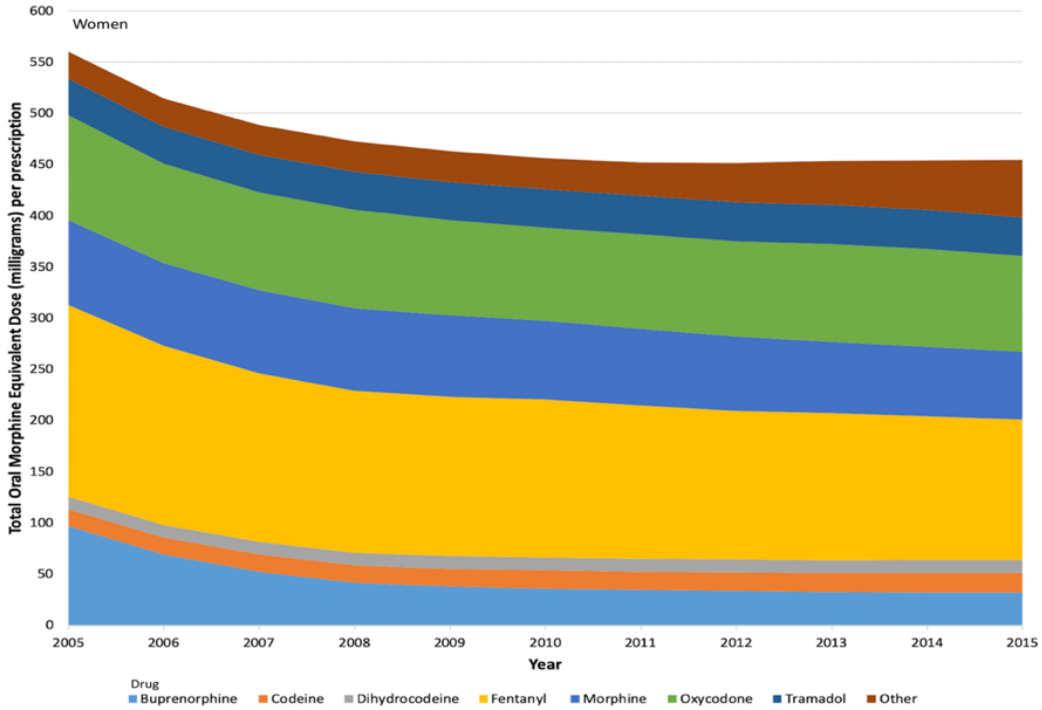


Figure 5.7: Trends in Oral Morphine Equivalent Dose (milligrams) per prescription issued to women and stratified by drug

Statistically significant difference was demonstrated in the $OMEQ_e$ per prescription of the different medicines prescribed to men (Kruskal-Wallis, $p<.001$, $\eta^2= 0.958$, $d_{Cohen}= 9.525$). $OMEQ_e$ per prescription for weak opioids codeine, dihydrocodeine and tramadol were significantly lower than for strong opioids morphine, oxycodone and fentanyl (Appendix D).

There were also statistically significant differences in the $OMEQ_e$ per prescription issued by drug to women (Kurskal Wallis, $p<.001$, $\eta^2= 0.919$, $d_{Cohen}= 6.753$). Codeine and dihydrocodeine had significantly lower $OMEQ_e$ per prescription compared to strong opioids, confirmed by post-hoc testing (Appendix D).

High dose opioid analgesic products (>120mg $OMEQ_e$) were also analysed by gender (Appendix D).

5.5.4 Differences in oral morphine equivalent dose by deprivation

The most deprived areas of Wales received 100,711,696 milligrams more $OMEQ_e$ compared to the least deprived between 2005 and 2015 (Table 5.7**Error! Reference source not found.Error! Reference source not found.**). The most

deprived areas in Wales had prescriptions issued totalling 28.4% of the total $OMEQ_e$ issued in the country compared to 12.2% of the total $OMEQ_e$ being issued in the least deprived areas. Total $OMEQ_e$ issued in the most deprived areas remained more than twice that in the least deprived areas throughout the 11 years examined (Figure 5.8**Error! Reference source not found.**).

Table 5.7: Trends in total oral morphine equivalent dose prescribed stratified by deprivation (Welsh Index of Multiple Deprivation) and adjusted to population

Year	Estimated oral morphine equivalent dose (milligrams) per 1,000 population				
	WIMD1	**WIMD2**	**WIMD3**	**WIMD4**	**WIMD5**
Total prescribed 2005-2015	176,824,265	146,459,878	129,880,669	93,691,687	76,112,569
2005	21,757	18,203	17,108	12,242	9,381
2015	43,176	35,475	32,564	23,534	17,557
Rate change (%) 2005-2015	98.4	94.9	90.3	92.2	87.2
Spearman's r, p-value*	>.999, <.001*	>.999, <.001*	>.999, <.001*	>.999, <.001*	>.999, <.001*

WIMD1 = most deprived, WIMD5 = least deprived. *p-value <0.05 = statistically significant. Annual results in Appendix D

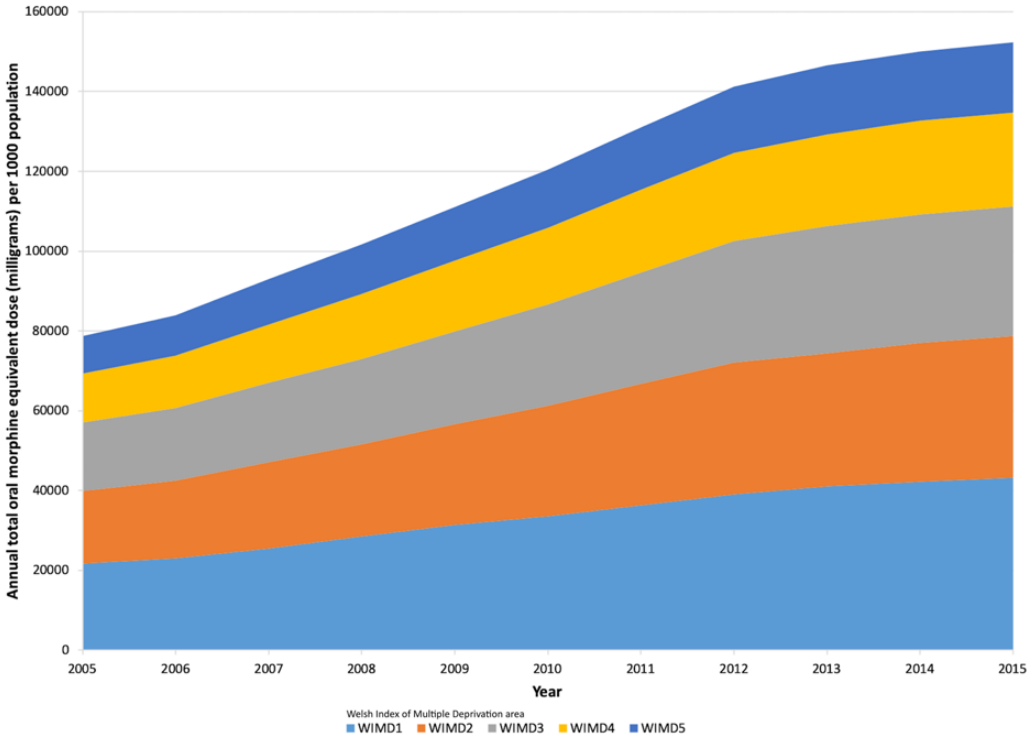


Figure 5.8: Trends in $OMEQ_e$ (milligrams) per 1,000 population, stratified by deprivation using the Welsh Index of Multiple Deprivation 2011 (WIMD2011)
WIMD1 = most deprived, WIMD5 = least deprived

All areas were noted to have had large increases in $OMEQ_e$ per 1,000 population prescribed over the 11 years examined with near doubling in annual totals by 2015 (Table 5.7**Error! Reference source not found.Error! Reference source not**

found.). An inverse relationship between deprivation quintile and percentage increase in opioid burden ($OMEQ_e$ per 1,000 population) was noted (Table 5.7)**Error! Reference source not found.**.

A Kruskal-Wallis analysis demonstrated a statistically significant difference ($p<.001$, $\eta^2= 0.601$ $d_{Cohen}= 2.456$) in the total $OMEQ_e$ (milligrams) prescribed across the five areas of deprivation in Wales. Post-hoc testing confirmed statistically significant differences between the three most deprived areas (WIMD1 to WIMD3) and the least deprived (WIMD5) and WIMD4 and the most deprived area (Appendix D). Similar differences were noted between quintiles with an overall statistically significant difference by Kruskal-Wallis analysis ($p<.001$, $\eta^2= 0.61$, $d_{Cohen}= 2.503$) between $OMEQ_e$ per 1,000 population (Appendix D).

$OMEQ_e$ per prescription were statistically the same across all levels of deprivation (Table 5.8) between 2005 and 2015 (Kruskal-Wallis p=0.262). Even so, the greatest percentage change in $OMEQ_e$ per prescription was seen in WIMD1 areas. As with earlier presented results, increasing deprivation was associated with greater percentage increase in $OMEQ_e$ per prescription and per person (Table 5.8).

Table 5.8: Trends in oral morphine equivalence stratified by deprivation (Welsh Index of Multiple Deprivation WIMD2011) and examined by dose per prescription and dose per person

Oral morphine equivalent dose (milligrams) per prescription					
Year	**WIMD1**	**WIMD2**	**WIMD3**	**WIMD4**	**WIMD5**
2005	22	24	24	25	24
2015	31	32	33	33	30
Rate change (%) 2005 – 2015	41.0	36.3	33.1	28.9	27.9
Spearman's r, p-value*	0.998, <.001*	0.993, <.001*	0.977, <.001*	0.995, <.001*	0.986, <.001*
Oral morphine equivalent dose (milligrams) per person receiving prescriptions					
2005	96	99	98	93	80
2015	173	169	161	151	128
Rate change (%) 2005 – 2015	79.2	70.2	64.7	61.3	60.2
Spearman's r, p-value	>.999, <.001*	>.999, <.001*	>.999, <.001*	>.999, <.001*	>.999, <.001*

WIMD1 = most deprived, WIMD5 = least deprived. *p-value <0.05 = statistically significant. Annual data in Appendix D.

Differences between quintiles were statistically significant (Kruskal-Wallis $p<0.05$, $\eta^2= 0.141$ $d_{Cohen}= 0.811$) for $OMEQ_e$ per person (Table 5.8). Post-hoc

analysis only confirmed statistically greater $OMEQ_e$ per person in the two most deprived quintiles, compared to the least deprived (Appendix D).

Oral morphine equivalent dose per person appeared similar in 2005, with the highest figure seen in WIMD2 areas and the lowest in the least deprived, at that time (Table 5.8). By the end of the study, the highest $OMEQ_e$ per person was noted in the most deprived areas due to a 79.2% increase over the 11 years. In 2015, there was 35% less $OMEQ_e$ prescribed per person in WIMD5 areas, compared to WIMD1 areas of Wales (Table 5.8**Error! Reference source not found.**).

5.5.4.1 Differences in high dose oral morphine equivalent dose by deprivation

Prescription opioid products which, based on the recommended dose, provide an $OMEQ_e$ of 120mg or higher totaled 146,289,419 milligrams between 2005 and 2015. This equates to 23.5% of the total $OMEQ_e$ prescribed (total =622,969,068 milligrams) in that time. Spearman's r correlations were very strong for all quintiles, confirming the increases in $OMEQ_e$ over the study period (Appendix D).

Table 5.9: Trends in total oral morphine equivalent dose of 120 milligrams or higher prescribed stratified by deprivation (Welsh Index of Multiple Deprivation) and adjusted to deprivation quintile population.

Year	Total oral morphine equivalent dose per 1,000 population for products of over 120mg $OMEQ_e$				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
Total prescribed (mg) 2005-2015	37,943,319	32,622,635	33,344,376	25,420,454	16,958,635
2005	3092	2561	3058	2515	1459
2015	11574	9863	9853	7171	4487
Rate change (%) 2005 – 2015	274.3	285.0	222.2	185.1	207.6
Spearman's r, p-value*	>.999	0.973	>.999	0.864	>.999
	<.001*	<.001*	<.001*	<0.010*	<.001*

WIMD1 = most deprived, WIMD5 = least deprived. *p-value <0.05 = statistically significant. Annual data in Appendix D

The total $OMEQ_e$ prescribed from high dose products were markedly different in the different areas of deprivation (Figure 5.9). The most deprived (WIMD1) areas of Wales had 27.4% of the total $OMEQ_e$ from ≥120mg products over the study period, similar to the distributions seen for all opioid prescribing (Chapter 4).

There was a significant difference between $OMEQ_e$ from products with ≥120mg $OMEQ_e$ noted between quintiles (Kruskal-Wallis, $p<0.01$, $\eta^2= 0.262$, $d_{Cohen}= 1.191$), although post-hoc analysis confirmed only statistically lower $OMEQ_e$ in the least deprived quintile (WIMD5) compared to the three most deprived (WIMD1 to WIMD3) (Appendix D). Large percentage increases in prescribing rates of high dose products were confirmed by very strong Spearman's correlations between $OMEQ_e$ and time (Table 5.9**Error! Reference source not found.**).

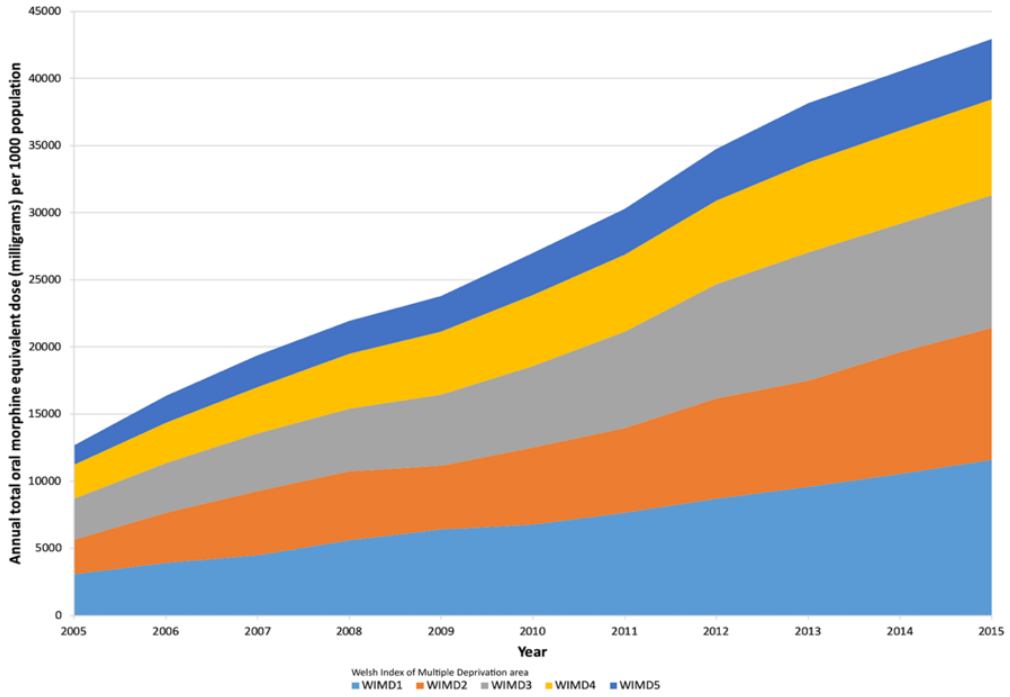


Figure 5.9: Trends in $OMEQ_e$ of 120 milligrams or higher per 1,000 population, stratified by deprivation using the Welsh Index of Multiple Deprivation 2011 (WIMD2011)
WIMD1 = most deprived, WIMD5 = least deprived

As with the totals of $OMEQ_e$ for any opioids, the highest rates of prescribing per 1,000 population were noted in the most deprived areas of Wales (Table 5.9). Oral morphine equivalent doses from products with a daily dose of ≥120mg, in WIMD1 areas were more than double those seen in WIMD5 areas, throughout the 11 years examined with the difference between those two groups increasing slightly over that time (Figure 5.9**Error! Reference source not found.**). As for total $OMEQ_e$ from high dose products, there were significant differences between totals in each quintile (Kruskal-Wallis $p<0.01$, $\eta^2= 0.29$, $d_{Cohen}= 1.279$),

although statistically, $OMEQ_e$ in WIMD1 to WIMD3 were significantly higher than in WIMD5 quintile areas, but no other differences were detected (Appendix D).

5.5.5 Comparison of prescription numbers and $OMEQ_e$

When percentage contributions of prescriptions and $OMEQ_e$ were compared, discrepancies were revealed. Codeine prescriptions accounted for over half of all prescriptions per 1,000 population over the study period. This translated however, to around 35% of opioid burden measured by $OMEQ_e$ (Figure 5.10**Error! Reference source not found.**). Similarly, dihydrocodeine took a greater percentage of prescription numbers than opioid burden. Tramadol, which in this study was classified as a weak opioid, (Section 2.6.3) had a higher opioid burden by $OMEQ_e$ than implied by the number of prescriptions per 1,000 population. All strong opioids and 'other' opioids were disproportionately represented in terms of prescription numbers compared to opioid burden (Figure 5.10**Error! Reference source not found.**).

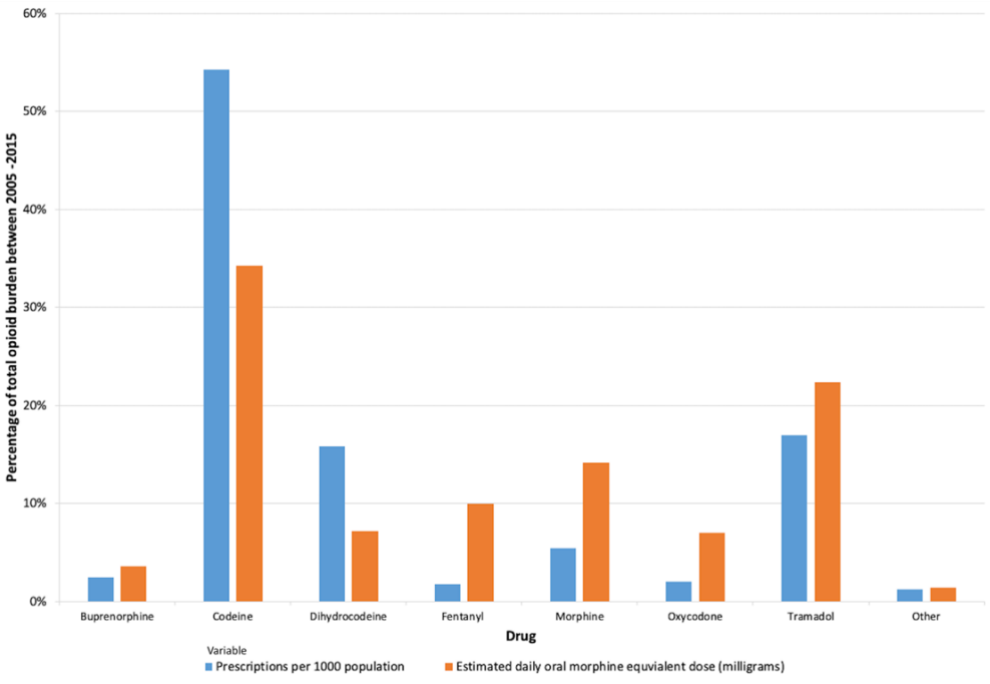


Figure 5.10: Comparison of the percentage contribution of each opioid prescribed by total prescriptions issued and total daily $OMEQ_e$ dose (mg) in Wales between 2005 and 2015

Examining the shape of trend graphs for the 11 years of the study, demonstrated for all opioids, a continuing but slowing increase in $OMEQ_e$ despite a plateauing of prescriptions being issued (Figure 5.11**Error! Reference source not found.**).

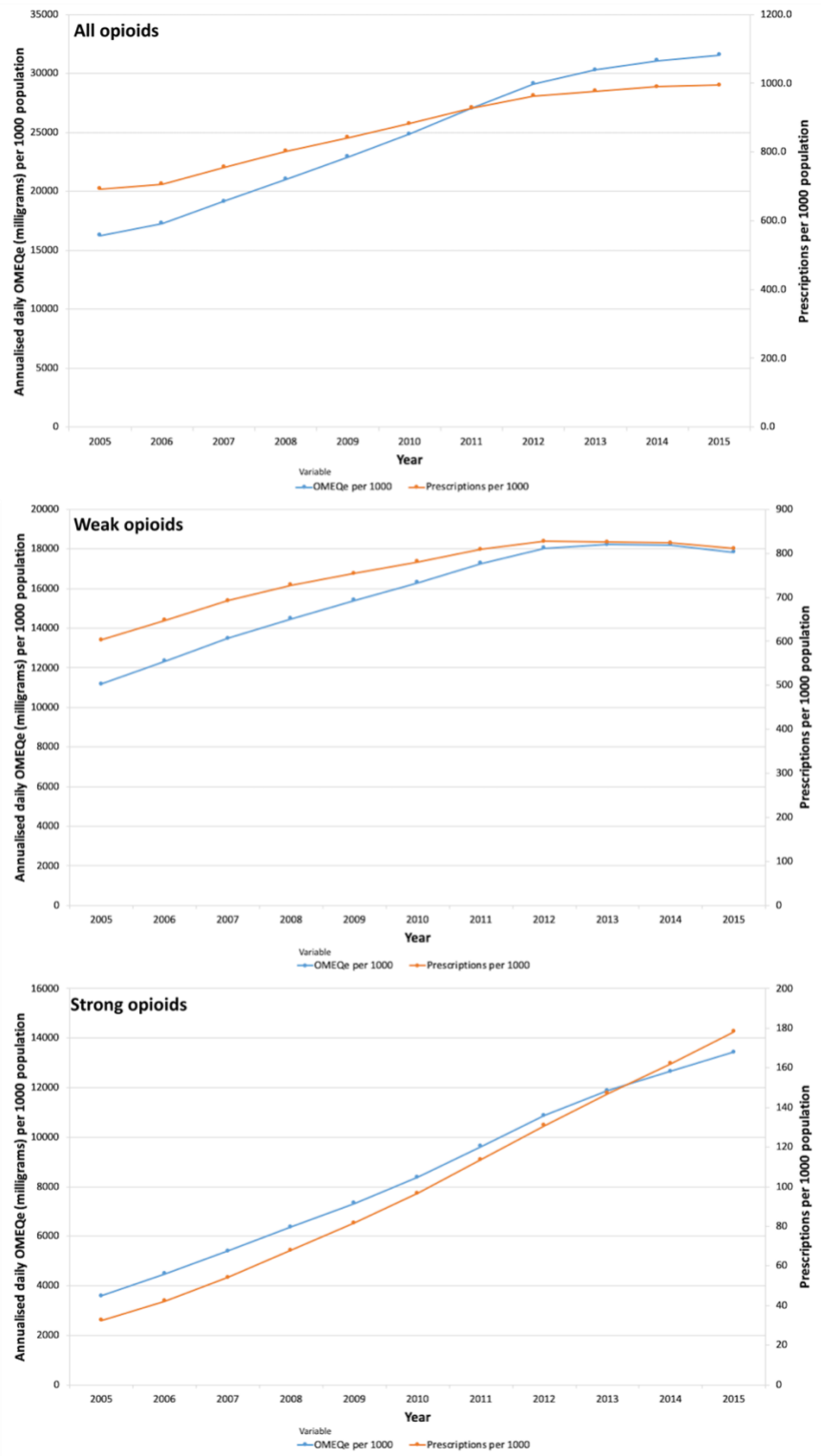


Figure 5.11: Trends in oral morphine equivalence compared to number of prescriptions issued per 1,000 population between 2005 – 2015

Strong opioid $OMEQ_e$ increases were starting to decelerate toward the end of the study compared to a continued increasing trend in prescription numbers (Figure 5.11**Error! Reference source not found.**). In contrast, weak opioids trends looked the same for prescriptions and $OMEQ_e$, both seemingly peaking between 2012 and 2013 and starting to reduce at the end of the study period.

5.6 Discussion

5.6.1 Summary and reflection on findings

The results presented in this chapter reinforced the trends in prescribing already discussed (Section 3.6.1 and Section 4.6.1). Namely, a large increase in prescriptions issued between 2005 and 2015. What this part of the study added was the detail that more than half of those prescriptions were for a single drug, codeine. This finding reveals prescribing is dominated by weak opioid prescriptions. Whilst codeine increased both in the number of prescriptions and $OMEQ_e$ over the study period, there was little difference in the dose per prescription. This was perhaps expected, given codeine is so widely prescribed, prescribers are likely to be confident about 'normal' dosing ranges. A similar pattern was seen with tramadol, where a small reduction in prescriptions issued was noted, followed by a reduction in $OMEQ_e$ towards the end of the study period. Unlike many other opioid analgesics, both drugs have recommended maximum daily doses stated in reference sources such as the BNF (BNF: British National Formulary - NICE. 2021). Strong opioids all showed large percentage increases in prescriptions and $OMEQ_e$ doses. Morphine was by far the most burdensome strong opioid although it had lower average doses per prescription than other strong opioids, such as oxycodone and fentanyl. Influence on prescribing choices is discussed in more detail in Chapter 6**.**

The reasons for high dose opioid prescribing could not be elucidated from data available for this study but is certainly something which warrants further investigation. In this chapter, increasing numbers of prescriptions were associated with a small reduction in the $OMEQ_e$ overall, although the number of higher dosed, strong opioids increased significantly. This was perhaps expected

from previous results (Section 3.6.7 and Appendix G), where weak opioid analgesics such as codeine and tramadol predominated at all durations. However, data also signaled a trend of strong opioids being increasingly represented as prescribing persistence rose (Appendix G). An example of this would be fentanyl, a drug that is not commonly prescribed. When it is, however, it appears to be prescribed at higher doses compared to other strong opioids, as demonstrated by a disproportionate $OMEQ_e$ compared to the number of prescriptions issued. This might point towards a lack of familiarity with dosing of non-morphine strong opioids and therefore, could support the wider use of OMEQ to illustrate prescribing data, where prescribers might contextualise dose choices more effectively. There was an increasing trend in ≥120mg $OMEQ_e$ dosing of morphine and oxycodone, despite mounting evidence of the harms caused when that limit is exceeded.

Differences in prescription numbers for each drug analysed and subsequent $OMEQ_e$ were predictable, when examined by gender, with women receiving more prescriptions and being exposed to a greater $OMEQ_e$ burden overall. However, men received higher doses per prescription, which, whilst not statistically significant for all drugs analysed, was still perhaps unexpected. Added to this was the finding that again, overall prescription durations were slightly longer for men than women. A reflection on these results is based on the perception that men are less likely to present with pain, than women. Is there an underlying assumption on the part of prescribers, that, when men present, it must be significant and therefore warrants higher doses or 'stronger' analgesics? Conversely, is it suggestive women are expected to tolerate higher levels of pain? Gender differences in opioid prescribing have been discussed already in this thesis (Section 1.8, Section 3.6.5 and Section 4.6.3) and the discrepancies raised by the results in this chapter reinforce the need for more research.

The major finding from comparing prescription numbers to $OMEQ_e$ is the potential underestimation of opioid burden if only prescription numbers are used. Especially pertinent are products such as transdermal fentanyl or

buprenorphine, where prescribers may be less familiar with the units of dosing. The result appears to be a disproportionate contribution to overall opioid burden based on relatively small prescription numbers. It perhaps suggests OMEQ is a more relatable measure of opioid burden and the added context it provides would be better understood by prescribers. The likelihood, however, is a combination of different measures are needed to provide the most complete picture of prescribing, over time. It is necessary to undertake further research on the measures of prescribing used in practice. As prescription numbers appear to be reducing, this study has demonstrated an increase in longer-term, higher dosed opioids, which are associated with much higher risks of harm. It could be too easy to assume that lowering the number of prescriptions lowers to burden on individuals or communities, but this may not be the case at all.

5.6.2 Comparison with the literature

5.6.2.1 Choice of opioid

Patterns of opioid use vary throughout the UK (Zin et al. 2014; Mordecai et al. 2018). Analgesic prescriptions dispensed in England between 1998 and 2017 revealed patterns of prescribing that this study upheld (Curtis et al. 2019). As in this study, codeine containing products were the most frequently prescribed analgesics, more so following the removal of co-proxamol/dextropropoxyphene from the UK market in 2005. Bedson et al. (2013) described a rapid increase in the prescribing of weak opioids (from 831 to 1021 prescriptions per10,000 people) such as co-codamol 8/500 following MHRA recommendations to stop co-proxamol and selective-anti-inflammatory analgesics in 2004 and 2005 (Bedson et al. 2013). During the same period, a reduction in moderate analgesics (from 614 to 393 prescriptions per 10,000 people) including codeine up to 20mg per dose, was described.

The results of TOPAS and Bedson's work has been corroborated by a large analysis where codeine prescribing increased by 5 times between 2006 and 2017 (Jani et al. 2020). Unlike TOPAS, Curtis separated co-products (where an opioid is combined with a non-opioid, commonly paracetamol) from prescriptions for the

opioid alone, revealing co-codamol (codeine and paracetamol) as the most frequently prescribed product. Scottish data showed a large increase in opioid analgesic prescriptions between 1995 and 2012 (Ruscitto et al. 2015). In 2010, codeine, tramadol and dihydrocodeine were the three most frequently prescribed medicines, as in the results presented here, with morphine by far the most frequently prescribed strong opioid (Ruscitto et al. 2015). Morphine was also shown to be prescribed more than other strong opioids between 2000 and 2010 in England and Wales, although oxycodone had a much higher percentage increase over that time (Zin et al. 2014).

TOPAS data would have demonstrated the same outcome, had data been presented separately. However, the aim was to analyse which opioid drugs were contributing to analgesic burden, regardless of the product used. Welsh data claimed tramadol accounted for up to 43% of opioid prescribing in 2012 (Welsh Analytical Prescribing Support Unit 2013) leading to a big campaign to reduce tramadol prescribing. However, data used to write the report, did not include co-products such as co-codamol, thus hugely underestimating the contribution of codeine to the overall prescribing burden in the country. Co-codamol was the 9th most frequently prescribed medicine in Wales, with more than 1.8million prescriptions issued in 2019-20 (Welsh Government 2020), clearly demonstrating the importance of it, in terms of prescribing burden, analgesic or otherwise. Codeine prescribing has been shown to predominate prescribing in the UK generally (Ashaye et al. 2018; Curtis et al. 2019). The COPERS trial (2018) examined opioid prescribing to people living in England with chronic musculoskeletal pain as a result of conditions such as osteoarthritis, back pain and fibromyalgia (Ashaye et al. 2018). Of the 703 participants recruited, 59% (413 individuals) were prescribed opioid analgesics over a year period. Of those, 53% (1768 of 3319 prescriptions) were for strong opioids like morphine or oxycodone. As in Wales, the most frequent prescription was for codeine (47%), tramadol accounted for 26% and morphine for 9% of prescriptions issued in that time (Ashaye et al. 2018) giving a similar picture to that described in the TOPAS study.

Different choices of opioids prevail outside of the UK. For example, hydromorphone is commonly prescribed in North America. One analysis of commercially insured patients noted 78.8% of all new prescriptions were for hydromorphone (Kern et al. 2015), compared to less than 0.01% of prescriptions examined during the 11 years of this study. Oxycodone, has predominated north American opioid prescribing for many years now (Fischer et al. 2014; Gomes et al. 2014) and has generally been considered the main source of the resulting problems of high prescribing and overdoses (Dhalla et al. 2011; Mulvihill et al. 2016). A comparison of oxycodone prescribing trends in the USA and Europe demonstrated over 10 years, oxycodone increased from 60mg to 175mg per capita in the USA, compared to 0 to 10mg per capita in Europe (Meyer et al. 2020). Prescribing in Australia is more similar to the UK, with codeine the most common opioid overall, but oxycodone is more regularly used than morphine (Karanges et al. 2016). Scandinavia uses several opioids not available in the UK, such as ketobemidone and nicomorphine which have accounted for a reasonable portion of their prescribing (Jarlbaek et al. 2005). What has been shown commonly throughout Europe however, is a rising use of oxycodone, fentanyl and tramadol (Hamunen et al. 2012; Palmaro and Lapeyre-Mestre 2015; Musazzi et al. 2018; Bosetti et al. 2019). This is often flagged as a concern due to the links of oxycodone and fentanyl with the opioid crisis in north America (Cicero et al. 2007; Kenan et al. 2012; Gomes et al. 2017). Whilst this study and others in the UK have also observed substantial increases in oxycodone prescribing in particular (Zin et al. 2014; Mordecai et al. 2018; Jani et al. 2020), levels have not reached those of morphine, as has been observed elsewhere.

5.6.2.2 Comparison of trends in opioid burden

To date, the largest UK-based examination of opioid prescribing by OMEQ suggested opioid burden was under-represented when only prescription numbers were used (Curtis et al. 2019). Curtis and colleagues demonstrated that a 34% increase in prescriptions issued between 1998 and 2016 resulted in a 127% increase in OMEQ burden (Curtis et al. 2019). Although different methods

of calculating OMEQ were used in the analysis presented here, a similar disparity was noted. A 44% increase in prescription numbers correlated to a 95% increase in OMEQ, albeit over a shorter timescale.

Analysis of 43 months prescribing data in England revealed tramadol to be responsible for the highest level of prescribing in OMEQ terms. Tramadol accounted for around 34% of opioid burden (Mordecai et al. 2018), which, is similar to the proportion of opioid burden codeine contributes in Wales. Curtis et al. (2019) did not provide data on each drug or products' OMEQ increase over time, however, the shape of trend graphs implied codeine, tramadol and morphine OMEQs increased until 2015 before starting to slowly reduce (Curtis et al. 2019). The proportions of these three opioids appeared like those noted in Wales.

Fentanyl was discovered to account for the highest proportion of high dose opioid prescribing (>120mg OMEQ) in England between 1998 and 2017 (Curtis et al. 2019), which followed a trend first described in 2014 (Zin et al. 2014). The TOPAS study demonstrated a different outcome, with morphine responsible for the largest $OMEQ_{e,}$ which continued to increase throughout the period of analysis.

Jani and colleagues (2020) examined opioid dosing changes over two years, at individual patient level (Jani et al. 2020). An increase in OMEQ over a year was reported in a relatively small proportion of people previously started on <50mg OMEQ with the majority (88.6%) stopped. Of those initiated on doses of 50-119mg OMEQ, reportedly 13.4% had a dose escalation to >120mg OMEQ within a year, although the majority (86.7%) were reduced or stopped. Of people commenced on >200mg OMEQ, whilst a small proportion of the total (1,446 of 1,925,944 people), had 45.4% remaining on that level of dosing at 6 months, although the percentage remaining on it, fell to 18.7% at 2 years (Jani et al. 2020b). This particular aspect of prescribing was not examined here. However, the implication of Jani et al.'s findings in addition to those presented here,

intimates the rising annual trend in $OMEQ_e$, is less likely due to individuals having doses increased and more likely due to an increasing number of people being started on higher doses (Jani et al. 2020).

Mordecai et al. (2018) included buprenorphine and methadone in their analysis, resulting in them being marked as major contributors to opioid burden (Mordecai et al. 2018). Both drugs are used at high OMEQ, primarily for substance misuse management rather than analgesia. Methadone and buprenorphine products used in substance misuse, were removed from the $OMEQ_e$ analysis, to try to form the best reflection of analgesic opioids. Methadone tablets were included in the analysis but contributed very little to overall burden, as would be expected in analgesic terms.

Increases in opioid burden have been reported across Europe. A 187% increase (from 36.0mg to 103.4mg OMEQ per capita) was reported between 2000 and 2015 in Poland. This was substantially less than estimated in this study using $OMEQ_e$ between 2005 and 2015 (estimated 16mg to 32mg over the period). However, the values are likely to be underestimated due to the lack of complete data. When opioid prescribing was compared between seven European countries using a DDD per 1,000 inhabitants measure, the UK was shown to have twice the rate of weak opioid prescribing and at least three times the rate of strong opioid prescribing than the others (Hider-Mlynarz et al. 2018). Based on the data presented, DDD per 1,000 inhabitants in the UK were reportedly almost equal for weak and strong opioids (approximately 51 DDD per person per day for weak and 48 DDD per person per day for strong opioids) (Hider-Mlynarz et al. 2018). While there are difficulties in directly comparing studies where different measures are used importantly is similar trends have been seen in many countries, with strong opioid consumption rising more quickly than weak opioids over time (Dzierżanowski and Ciałkowska-Rysz 2017).

Australia has seen large increases in opioid prescribing also. In 2013, an estimated 481mg OMEQ per person was sold (Degenhardt et al. 2016). Trend

analysis between 1990 and 2014, demonstrated large percentage increases although using a non-OMEQ measure, the rise was from around 5 to 17 DDD per 1,000 population over that time (Karanges et al. 2016). As different opioids were included, it is not possible to calculate the OMEQ doses or compare to this study's findings with any accuracy. The trends noted however, are consistent with these findings and those already discussed (Section 3.5.2 and Section 4.5.1.1).

Previous studies have observed gender, age and socio-economic deprivation to be implicated for higher OMEQ doses of opioids (Spooner 2016; Todd et al. 2018; Macfarlane et al. 2020; Nowakowska et al. 2020; Richards et al. 2020). Studies were not found which examined those trends over time, in the way presented here. A systematic review of factors associated with high dose opioid prescribing (>90mg OMEQ per day) included being male (RR 1.21) and being unemployed (RR 1.44) which is often used as a proxy-measure of socioeconomic deprivation (Richards et al. 2020a).

This study substantiated the results, as increasing deprivation was demonstrated to be associated with higher $OMEQ_e$ burden and a greater percentage of high dose prescribing (>120mg $OMEQ_e$). Empirically, overall $OMEQ_e$ burden was significantly higher for women, according to the findings, other than for morphine and oxycodone. $OMEQ_e$ per prescription for strong opioids were significantly higher for men in this study, however. Higher $OMEQ_e$ was used to define 'high dose', but it appears correct to suggest men were more likely to receive a prescription for a strong opioid or to receive a higher dose. Prescribing in rural, less affluent areas of Australia with large male populations, has been observed to yield higher OMEQs (Degenhardt et al. 2016), which further corroborates the TOPAS results presented in this chapter and elsewhere (Section 3.5.3 and Section 4.5.2).

Substantial increases in opioid prescribing, with higher levels in more deprived populations have been reported in other parts of the UK (Mordecai et al. 2018)

and internationally (Joynt et al. 2013; Wagemaakers et al. 2017). Increased levels of prescribing in areas of high socio-economic deprivation has been linked to greater reported pain intensity (Todd et al. 2018). However, limited evidence supports the notion that opioids are effective at reducing pain, particularly in the longer term (Furlan et al. 2006; Chaparro et al. 2014). High-dose opioids (above 120mg OMEQ) have been associated with increased levels of pain (Cohen et al. 2008). In the context of this and previous studies (Mordecai et al. 2018; Todd et al. 2018), the implications of increased opioid prescribing in more deprived areas are concerning. It exposes the most vulnerable people to higher levels of medicines, that may be ineffective at best and could cause additional health and well-being complications (Els et al. 2017).

However, similarities were demonstrated in the trends seen in age-group prescribing, where people aged 45 years and over had a significantly higher incidence of long-term opioid prescribing (Chapter 3 and Appendix G). Lalic et al. (2018) found people aged over 75 years were at least twice as likely to be persistently prescribed opioids, corroborating the findings presented in this thesis, that overall prescribing persistence increased with rising age (Lalic et al. 2018).

Few studies have examined gender trends in opioid use duration, despite it being widely acknowledged women are more likely to receive long-term opioid treatment (Darnall et al. 2012). One study, however, found women of all age groups had consistently higher levels of long-term prescribing than men (Bedson et al. 2016), which reflects this study's findings.

This study demonstrated weak opioids and codeine especially, were used most frequently at all durations of prescribing analysed, although the use of strong opioids increased with rising prescribing persistence (Chapter 3 and Appendix G). A previous review of prescribing in the UK and Germany, demonstrated codeine to be the most prescribed opioid in the UK (Chevalier et al. 2014). This was consistent with the findings of Kern et al. (2015), who observed weak opioids

were prescribed chronically, twice as often as strong opioids. The choice of opioids in either category was different to those in this study however, with hydrocodone (not available in the UK) rather than codeine being the most frequently prescribed weak opioid. Oxycodone was prescribed long term, twice as often as any other strong opioid in the same study (Kern et al. 2015), whereas morphine was most used in Wales. Durations were not significantly different between different strong opioids in this study. Bedson and colleagues (2016), examining prescribing duration, noted 20% of people receiving opioid prescriptions for more than 2 years, received modified release strong opioids (Bedson et al. 2016). This confirms the results of TOPAS, showing an increased likelihood of receiving strong opioids as total duration of opioid prescribing lengthens (Appendix G).

5.7 Conclusion

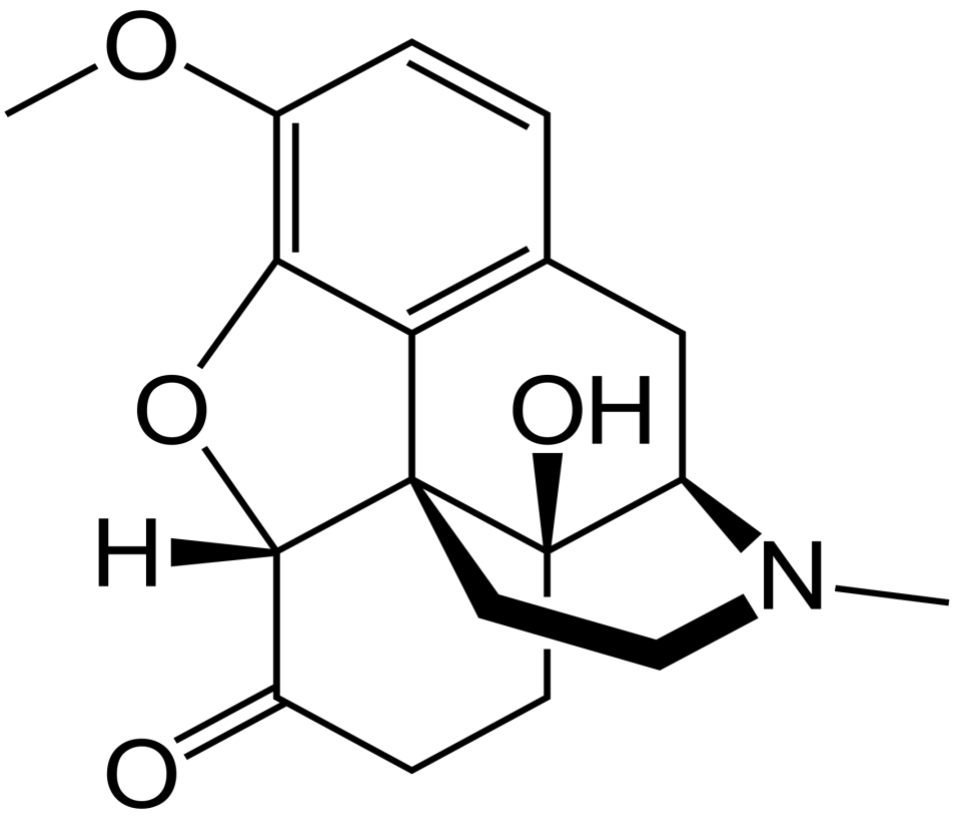
This is the first study that has examined burden in $OMEQ_e$ terms in Wales. Increasing numbers of prescriptions between 2005 and 2015, betrays the full extent of the opioid burden placed upon the Welsh population. Few UK based studies have studied OMEQ trends; although it is becoming more common place as researchers realise it is an effective means of providing contextualised data that can be used more easily in practice.

Whilst it was known that strong opioid prescribing has increased significantly in Wales since the beginning of the 2000's, this study reveals more about the nature of that increase. Whilst opioid analgesics of all strengths have increased, the implication of high levels of strong opioids, which carry a greater OMEQ burden per dose, is considerable. This is especially notable in areas of deprivation and in older people (results in Appendix D), both variables demonstrating large increases during the study period.

There is not a single measure of prescribing that provides sufficient information of risk. OMEQ is an estimated measure and so caution is required when applying it in clinical practise. The data used in this study was not wholly precise but

demonstrates that OMEQ offers an easily interpreted measure for assessing dose burden in practise, given its ability to place all opioids on an 'equal' footing. Caution does need to be applied, when using OMEQ within guidelines to ensure it is not assumed to be a completely accurate measure of effectiveness and safety. It seems sensible to suggest that in Wales, a method of combining OMEQ and prescribing persistence as a measure of monitoring opioid prescribing in real time should be sought. In addition, clinicians would benefit from clear guidance on initiating and reviewing opioids, considering the risks of both dose and duration to each individual . Whilst prescription numbers may have started to slowly decrease, data presented here, suggests the overall burden posed by opioids was still increasing in 2015. Prescribers and policymakers must not assume that a fall in prescription numbers alone is sufficient to reduce the risks of opioids.

Chapter 6
Time Series Analysis examining the effect of legislation and prescribing guidance on opioid prescribing in Wales



"They always say time changes things, but you actually have to change them yourself."
Andy Warhol

Chapter 6 – Time Series Analysis examining the effect of legislation and prescribing guidance on opioid prescribing in Wales

6.1 Chapter overview

Chapters 1 and 2 discussed the background to the research and explanation of the methods adopted in order to extract and analyse the data, respectively. Chapters 3 and 4 presented trend data for opioid prescribing in Wales, revealing large increases in rates between 2005 and 2015, disproportionately affecting women and people living in the most socioeconomically deprived areas of Wales. Chapter 5 examined trends by $OMEQ_e$ which demonstrated three drugs, codeine, tramadol and morphine were responsible for 70% of opioid burden in the study population. Again, gender and deprivation predominated in terms of associations with greater burden. Whilst overall opioid burden was higher in women, data suggested that men received higher doses of prescribed opioid analgesics. Chapter 6 builds on the previous chapters, by using time series analysis (TSA) to investigate the effect of legislative changes and the development of National Prescribing Indicators in Wales on the trends in opioid analgesic prescribing between 2005 and 2015.

6.2 Study objective to be addressed in this chapter

- To determine if general opioid prescribing trends were influenced by legislative or clinical guidance changes during the study period using time series analysis

6.3 Background

Time Series Analysis (TSA) is an established method in healthcare research and has been used to examine a range of issues related to analgesics (Chang et al. 2016; Gomes et al. 2017; Musazzi et al. 2018; Alexander et al. 2019;). Ranging from predicting prescription choice within an electronic prescribing system (Helgason 2008) to predicting whether an individual will respond to treatment (Alexander et al. 2019), TSA can be a useful tool on its own or in combination

with other analysis methods. The outcome of introducing new prescribing legislation and monitoring requirements has been studied using interrupted TSA as part of a trend analysis from Canada (Gomes et al. 2014) over a similar time span to TOPAS. Studies investigating the introduction of new opioid formulations of opioid medicines, specifically oxycodone have also used TSA, demonstrating changes in the choices being made by prescribers (Gomes et al. 2017; Musazzi et al. 2018). Interrupted TSA was also used to determine the effect of rescheduling hydrocodone on illicit opioid purchases in the USA in 2014 (Martin et al. 2018). It was planned as part of this study, to use TSA to create predictions of how prescribing might progress after the end of the study period (from 2016 to 2018) if no further changes were made to guidance or policy around the prescription of opioid medicines. No literature on using TSA to predict future opioid prescribing trends was found. However, TSA has been used to analyse changes in prescribing following the introduction of new products (Musazzi et al. 2018; Gomes et al. 2017; Puenpatom et al. 2012) with the actual trend noted compared to that predicted by the TSA.

As discussed in Section 1.11, guidelines and legislation introduced into the UK over the last 15 years, were designed to improve access to data and the quality and safety of prescribing practice (Baker 2004; National Institute for Health and Clinical Excellence 2008; Centre for Clinical Practice at NICE 2013; All Wales Medicines Strategy Group 2013). Despite this, as has been demonstrated in results presented in Chapter 3, Chapter 4 and Chapter 5, opioid prescribing trends in Wales appeared to be on an upwards trajectory for the majority of the study period. This chapter presents TSA as a method to analyse whether introducing legislation and guidelines which acted to manage prescribing of and rational use of opioid analgesics, affected prescribing in practice.

6.4 Method

6.4.1 Forms of time series analysis

Prescribing trend data can be considered a form of time series. Time series analysis (TSA) is a method of forecasting future values based on the known

pattern of past data (Beard et al. 2019). Interrupted TSA is a quasi-experimental means of examining the influence of an intervention on the time series being tracked. Time series analysis uses observations, in the case of TOPAS, the number of prescriptions issued each month, over successive time periods (each month) which allows a trend (the time series) to be seen. The high volume of data available from the SAIL databank potentially lends itself to TSA as each data point (month) contains a large amount of data on which to base the prediction for the next.

Two forms of TSA were used. The first was a continuous TSA, where monthly data points were plotted for the whole study period (Section 6.4.2) and an assessment was then made of whether the trend described had been affected by any of a number of 'interventions', which for this study, were legislative or prescribing advisories.

An interrupted TSA was also performed, to assess the impact of a specific intervention, namely the introduction of a national prescribing indicator for 2012 to 2013, which encouraged morphine as the strong opioid of choice (Section 1.11). Effects of the intervention on the number of strong opioid prescriptions issued were examined using the changes in the level and slope of the plotted data-series and their calculated statistical significance (Bernal et al. 2017; Hebert et al. 2021).

The interrupted TSA model used was:

$$Y = ß_0 + ß_1 * Time_1 + ß_2 * Intervention + ß_3 * Intervention * Time_2$$

Where Y is the number of prescriptions issued (prescribing rate) and $ß_0$ is the intercept (the number of prescriptions issued at the beginning of the study). ß1 represents the number of prescriptions issued per time unit (prescribing rate) prior to the intervention, ß2 is the level change that follows the intervention and $ß_3$ is the change in the trend (rate of prescribing) after the intervention. Time in

this equation refers to the elapsed time from the start of the study ($Time_1$) and after the intervention ($Time_2$) respectively.

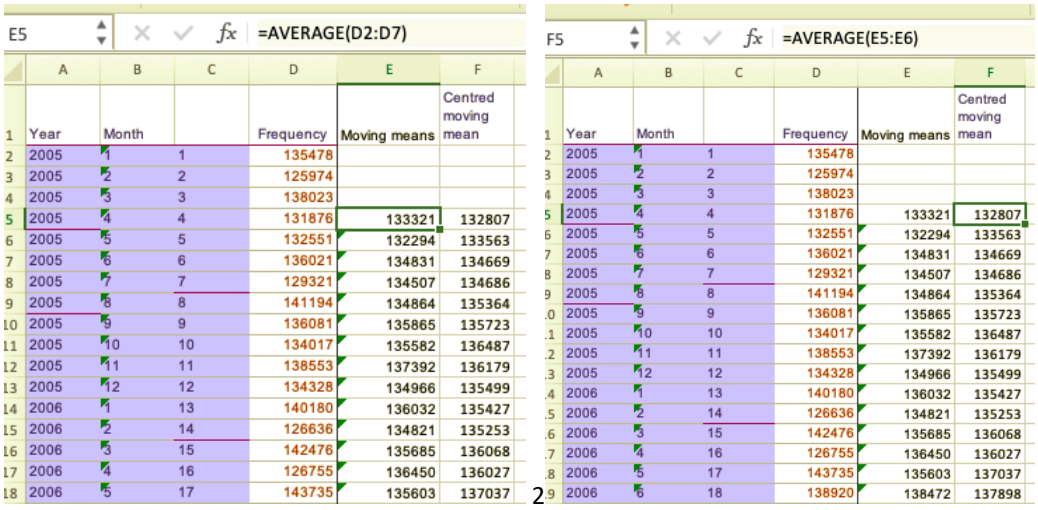
6.4.2 Calculating the moving mean and centred-moving mean for TSA

There is inherent random variation in data collected over time and methods are therefore, adopted in order to reduce or cancel the effects. An oft-used technique is 'smoothing', which, when properly applied, can clearly reveal the underlying trends, seasonal and cyclical components of the data. There are two general methods for smoothing, namely averaging methods and exponential smoothing methods. Simple averaging or using the mean of all past observations is effective for forecasting only in the absence of trends. Where trends are present, smoothing methods need to take them into account. To do this, smaller sets of data are averaged.

For this TSA, the moving means (MM) were calculated using 6 months of data (number of prescriptions issued) per set (Appendix E). The first set to be averaged were months one to six from 2005 (Figure 6.1). Six months of prescriptions were averaged, with the outcome being placed at the month-4 mark on the spreadsheet. The next MM was calculated from prescription numbers for months two to seven, with the outcome placed at month-5. This process was repeated for the rest of the eleven years of data, with the final value calculated at month-132.

This study, covering 11 full years of data, had an even number of datapoints (132 months). Using MM requires the calculated average to be placed in the middle of the time period being covered in order to produce the smooth plot required. Where there are an uneven number of data points, this is straightforward (e.g., if there are three timepoints, then the moving mean is placed at time point two). For this TSA, an additional smoothing technique was needed to take account of the even number of datapoints. Centred moving means (CMM) were calculated using pairs of consecutive moving means (Figure 6.1). The first CMM was

calculated as the average of MM1 and MM2, the second CMM was the average of MM2 and MM3 and so on.



	A	B	C	D	E	F
1	Year	Month		Frequency	Moving means	Centred moving mean
2	2005	1	1	135478		
3	2005	2	2	125974		
4	2005	3	3	138023		
5	2005	4	4	131876	133321	132807
6	2005	5	5	132551	132294	133563
7	2005	6	6	136021	134831	134669
8	2005	7	7	129321	134507	134686
9	2005	8	8	141194	134864	135364
10	2005	9	9	136081	135865	135723
11	2005	10	10	134017	135582	136487
12	2005	11	11	138553	137392	136179
13	2005	12	12	134328	134966	135499
14	2006	1	13	140180	136032	135427
15	2006	2	14	126636	134821	135253
16	2006	3	15	142476	135685	136068
17	2006	4	16	126755	136450	136027
18	2006	5	17	143735	135603	137037

	A	B	C	D	E	F
1	Year	Month		Frequency	Moving means	Centred moving mean
2	2005	1	1	135478		
3	2005	2	2	125974		
4	2005	3	3	138023		
5	2005	4	4	131876	133321	132807
6	2005	5	5	132551	132294	133563
7	2005	6	6	136021	134831	134669
8	2005	7	7	129321	134507	134686
9	2005	8	8	141194	134864	135364
10	2005	9	9	136081	135865	135723
11	2005	10	10	134017	135582	136487
12	2005	11	11	138553	137392	136179
13	2005	12	12	134328	134966	135499
14	2006	1	13	140180	136032	135427
15	2006	2	14	126636	134821	135253
16	2006	3	15	142476	135685	136068
17	2006	4	16	126755	136450	136027
18	2006	5	17	143735	135603	137037
19	2006	6	18	138920	138472	137898

Figure 6.1: Screenshot of Excel spreadsheet showing calculation of moving means (1) and centred moving means (2) for opioid prescriptions as part of time series analysis

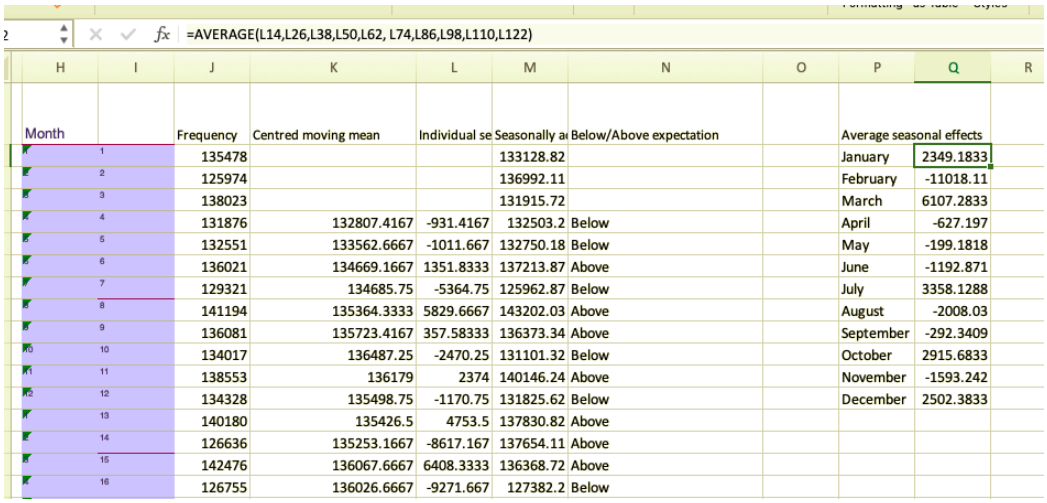
Once MM and CMM were calculated for each dataset, scatter plots were drawn using the raw data (frequency/number of prescriptions) and the moving mean values. A trend line was inserted using the centred moving mean values, which gave an indication of the trend over the period examined.

6.4.3 Seasonal adjustment

Seasonal variation can be due to specific events such as holidays or types of weather for example. It was examined for the TOPAS study in order to determine if there were any differences in the number of prescriptions issued, based on the time of year or the month of issue.

Individual seasonal effect (ISE) was calculated by subtracting the centred moving mean from the number of prescriptions issued in the corresponding month. Ten ISEs for each of the 12 months were used to calculate the average seasonal effect (ASE) for the number of prescriptions issued (Figure 6.2). Seasonally adjusted values (SAV) were calculated by subtracting the average seasonal effect from the actual number of prescriptions recorded. A determination of whether the SAV was above or below what might have been expected, based on previous prescribing trends, was made. If the value of subtracting the SAV from CMM was

less than zero, then the number of prescriptions issued were marked as less than expected. If the value was greater than zero, then the number of prescriptions were marked as above what would have been expected on the basis of previous prescribing patterns (Figure 6.2).



=AVERAGE(L14,L26,L38,L50,L62, L74,L86,L98,L110,L122)

Month	Frequency	Centred moving mean	Individual se	Seasonally a	Below/Above expectation	Average seasonal effects	
1	135478			133128.82		January	2349.1833
2	125974			136992.11		February	-11018.11
3	138023			131915.72		March	6107.2833
4	131876	132807.4167	-931.4167	132503.2	Below	April	-627.197
5	132551	133562.6667	-1011.667	132750.18	Below	May	-199.1818
6	136021	134669.1667	1351.8333	137213.87	Above	June	-1192.871
7	129321	134685.75	-5364.75	125962.87	Below	July	3358.1288
8	141194	135364.3333	5829.6667	143202.03	Above	August	-2008.03
9	136081	135723.4167	357.58333	136373.34	Above	September	-292.3409
10	134017	136487.25	-2470.25	131101.32	Below	October	2915.6833
11	138553	136179	2374	140146.24	Above	November	-1593.242
12	134328	135498.75	-1170.75	131825.62	Below	December	2502.3833
13	140180	135426.5	4753.5	137830.82	Above		
14	126636	135253.1667	-8617.167	137654.11	Above		
15	142476	136067.6667	6408.3333	136368.72	Above		
16	126755	136026.6667	-9271.667	127382.2	Below		

Figure 6.2: Screen shot of Excel spreadsheet showing calculation of average seasonal effect on the number of opioid prescriptions issued from Primary Care Practices registered with the SAIL databank

6.4.4 Predicting future issue of prescriptions

A trendline was added to the scatter plot of values and centred moving mean using Excel graphing. The coefficient of determination (R^2) was calculated for each trendline in order to decide how well the regression line might approximate the real values and consequently, the accuracy of predictions of future values. A coefficient of determination of >.999 means that a given month's number of prescriptions can explain 100% of the number of prescriptions issued in the following month. Consequently, the closer R^2 is to >.999, the better 'fit' of the trendline and it can be assumed that the subsequent predictions are of greater accuracy.

Predicting future values for the number of prescriptions that might be issued is based on the equation that describes the trendline e.g., for a second order polynomial trendline:

$f(x) = ax^2 + bx + c + ASE$

Where x is the time value, which in this study, is the month as a number based on January 2005 being equal to one and December 2015 being equal to 132. Consequently, predictions after the end of the study period in 2015 will use time values from 133. ASE is the average seasonal effect and a, b and c are coefficients generated by Excel when determining the trendline.

Whilst predictions using existing data have a measure of accuracy based on the coefficient of determination, predicting future events is likely to be less accurate unless the time series remains stationary. TSA with trends or seasonality are not considered stationary, as those shifts can affect the value at different times in the analysis.

For this study, the chosen intervention for the interrupted TSA was the introduction of the 2012 to 2013 NPI that aimed to increase the percentage of morphine as the total of all strong opioid prescribing. This was the first NPI that focussed on strong opioids, which were at the time, considered a bigger concern than overall opioid burden.

6.4.5 Legislation changes in the UK between 2005 and 2015

The major changes to legislation (Changes to the Misuse of Drugs Regulations 2001) as a result of the Shipman enquiry (NHS Prescription Services 2017) were (Figure 6.3):

1. 14 November 2005 – to allow computer generation of prescriptions (other than prescriber signature) and the computerisation of controlled drug registers for Schedule 1 and 2 drugs (Appendix E) (UK Government 2021).
2. 7 November 2006 – special forms for private controlled drug prescriptions (Schedule 2 and 3) and a central database to allow monitoring locally were introduced. Changes in collection arrangements of prescriptions, requiring a signature from the person collecting them from the dispensing pharmacy or on delivery if using a home-service. The validity of prescriptions for schedule 2, 3 and 4 controlled drugs was restricted to 28 days, meaning that

prescriptions needed to be dispensed and collected within 28 days from issue. A requirement was introduced for standard operating procedures to be in place and complied with for any healthcare provider keeping stocks of controlled drugs. Further recommendations were issued although not legislated, that no more than 30 days of medicines should be prescribed at one time (for schedule 2, 3 and 4 controlled drugs). Professional guidance was also reinforced that doctors should only prescribe controlled drugs for themselves or their family in exceptional circumstances.

3. 1 January 2007 – Designated bodies, such as Health Trusts and Health Boards became required to appoint an Accountable Officer to monitor the use of controlled drugs within their organisations or across a wider area (in the case of Health Boards).
4. 1 September 2007 – a requirement was introduced that dispensing contractors (e.g., community pharmacies) no longer had to retain private controlled drug prescriptions (Schedule 2 and 3) for 2 years, in order to allow them to submit the original prescriptions for reimbursement. Controlled Drug Accountable Officers were also responsible for appointing authorised witnesses to oversee the destruction of controlled drugs.
5. January 2008 – Suppliers of schedule 2 and 3 controlled drugs became obliged to provide information in regard of supplies of controlled drugs, where there was no prescription to be submitted. This legislative change also introduced more flexible arrangements in regard of the formatting of controlled drug registers, although the requirement for verifying the identity of someone collecting a schedule 2 medicine was still necessary.
6. 23 April 2012 – Nurse and Pharmacist Independent Prescribers became able to prescribe opioid medicines (other than diamorphine, cocaine and dipipanone for addiction)
7. 1 April 2013 – the Controlled Drugs (Supervision and Use) regulations were updated to reflect organisational changes within the National Health Service. It reiterated the need for organisations to appoint Accountable Officers for

Controlled Drugs but widened their potential 'reach' in terms of monitoring and investigating concerns.

8. 1 June 2014 – Tramadol was reclassified as a schedule 3 controlled drug although remained exempt from safe custody requirements.
9. 2 March 2015 – a new drug driving law came into force which made it a criminal offence to be in charge of a motorised vehicle with blood concentration levels above specified limits for named opioid analgesics and other prescribed and illicit drugs.
10. 1 June 2015 – Limited prescribing of scheduled opioid analgesics was allowed for independent physiotherapist and podiatrist prescribers. Under this legislation, it also became mandatory to use a standardised form for schedule 2 and 3 requisitions of controlled drugs.
11. July 2015 – a statutory instrument was introduced to allow electronic prescribing of schedule 2 and 3 controlled drugs under the Electronic Prescribing Service (EPS) structure in Primary and Community Care.

6.4.6 Prescribing and condition guidance

The National Prescribing Indicators for Wales and relevant NICE guidelines published within the study period 2005 to 2015 were (Figure 6.3):

12. 2008 – Osteoarthritis: National Clinical Guidelines for care and management in adults (NICE). Opioid analgesics were neither recommended for use or to be avoided. Prescribers were encouraged to consider paracetamol and NSAIDs (National Collaborating Centre for Chronic Conditions 2008).
13. 2009 – Low back pain: the acute management of patients with chronic (longer than 6 weeks) non-specific low back pain (NICE). The guideline included a recommendation for the short-term use of strong opioids to manage severe pain (National Institute for Health and Clinical Excellence 2008).
14. 2012-2013 – NPI Morphine as a percentage of strong opioid prescribing. Prescribers were encouraged to prescribe morphine first line where a strong opioid was required.

15. 2013 – Neuropathic pain: the pharmacological management of neuropathic pain in adults in non-specialist settings (CG173 – NICE). Discouraged the use of opioid analgesics other than tramadol for short-term, flare up management (Centre for Clinical Practice at NICE 2013).
16. 2013-2014 – NPI from the previous year was repeated.
17. 2014 – Osteoarthritis: care and management (CG177 – NICE). Suggests prescribers consider opioids but does not specify particular categories of medicines to consider (National Institute for Health and Care Excellence 2014).
18. 2014-2015 – NPIs set out to encourage the appropriate prescribing of all opioid-containing analgesics and three measures were set out. The first was total opioid prescribing by the number of items (prescriptions) issued per 1,000 patient units (as adjusted measure based on population and demographic e.g., age). The second measure was a repeat of the previous two year's morphine indicator. A third indicator was directed specifically at tramadol prescribing with the aim of reducing the number of daily defined doses (Nielsen et al. 2017) of tramadol products per 1,000 patients in each Health Board area.
19. 2015-2016 – NPIs were maintained morphine as a percentage of strong opioid prescribing and to reduce tramadol prescriptions as for 2014 to 2015.

The launch of each prescribing indicator was plotted on a time-series analysis of total opioid prescribing as a marker for the timing of reinforcement of advice and guidance around opioid prescribing during the study period.

6.4.7 Prescription charges

20. Prescription charges for medicines dispensed in Wales were abolished in April 2007 (National Assembly Government 2010) (Figure 6.3). Prior to that, around 50% of the population were entitled to free prescriptions due to exemptions such as age, low income or having certain medical conditions (National Assembly Government 2010).

6.5 Results

6.5.1 Legislation and guidance changes

Between 2005 and 2008, there was an 18% increase (from 1,613,417 to 1,904,351 prescriptions respectively) in the total number of opioid prescriptions issued annually. In the same period five pieces of legislation were introduced to Welsh law and prescription charges abandoned (Figure 6.3). Between 2008 and 2012, one further piece of legislation was introduced, and two NICE guidelines were published. Over the same period the number of prescriptions issued increased by 22% (from 1,904,351 to 2,318,407 prescriptions per year). In the last four years of the study, six pieces of legislation were introduced which concerned opioid prescribing, including the reclassification of tramadol as a controlled substance in 2014 (Figure 6.3).

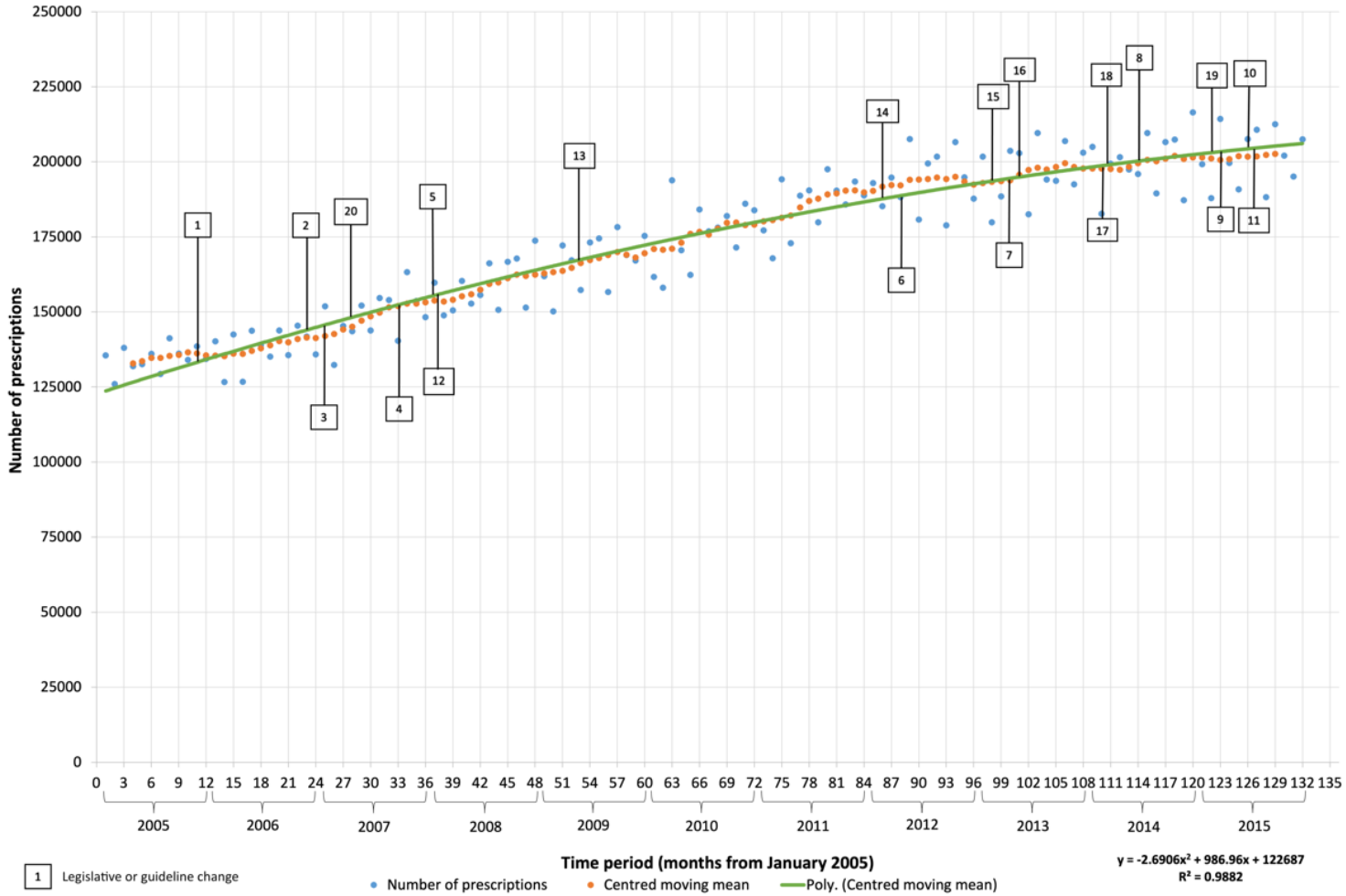


Figure 6.3: Monthly trend in the number of opioid prescriptions issued from Primary Care Practices who provide data to SAIL databank. Shown with a polynomial (x^2) 'best fit' trendline, R2=0.9882. Shown with time markers for legislation changes and National Prescribing indicators which included targets for reducing prescribing

NPIs introduced in 2012 and repeated every year thereafter, included opioid prescribing markers. Two NICE guidelines which included recommendations on opioid analgesics were issued in the final three years of the study. Between 2012 and 2015, the increase in the annual number of opioids was 4% (from 2,318.407 to 2,415,374 prescriptions per year, respectively).

6.5.2 Interrupted Time Series Analysis

A maximum likelihood (MLE) method or variable estimation was used rather than ordinary least squares (OLS) as MLE had a lower root mean squared error (RMSE) and corrected Akaike information criterion (AICc) and higher R-square (Table 6.1). That pattern of output indicates the MLE model was a better fit than the OLS.

Table 6.1: Output from testing for best-fit model of interrupted time series analysis

Maximum Likelihood Estimates			
SSE	3491395401	**DFE**	125
MSE	27931163	**Root MSE**	5285
SBC	2668.7667	**AIC**	2648.58709
MAE	4149.3777	**AICC**	2649.49032
MAPE	2.45605683	**HQC**	2656.78716
Log Likelihood	-1317.2935	**Transformed Regression R-Square**	0.9406
Durbin-Watson	1.9425	**Total R-Square**	0.9582
		Observations	132
Ordinary Least Squares Estimates			
SSE	8355585466	**DFE**	128
MSE	65278011	**Root MSE**	8079
SBC	2765.29901	**AIC**	2753.7678
MAE	6683.04306	**AICC**	2754.08276
MAPE	3.88787343	**HQC**	2758.45355
Log Likelihood	-1372.8839	**Total R-Square**	0.9001
Durbin-Watson	2.9599	**Observations**	132

Based on the parameter estimates derived, the model revealed a positive pre-intervention trend (Table 6.2). The intervention investigated (introduction of NPI for morphine as percentage of strong opioid prescribing, 2012 – 2013), was followed by a non-significant step-up in the number of prescriptions issued. The step up was not unexpected, given the preceding trend. The post-intervention trend demonstrated a reduction in the number of prescriptions being issued (Table 6.2).

Table 6.2: Results of interrupted time series analysis of opioid prescribing data

	Parameter estimates			
Variable	**Estimate (95% CI)**	**Standard Error**	**t Value**	**Approx Pr > |t|**
Intercept ($ß_0$)	127253	1266	100.51	<.0001
Pre-intervention trend ($ß_1$)	738.5126 (691.48 – 785.55)	23.9968	30.78	<.0001
Change in level ($ß_2$)	750.9560	1659	0.45	0.6516
Post-intervention trend ($ß_3$)	-500.3484 (-624.38 - -376.31)	63.2839	-7.91	<.0001
AR1	0.4526	0.0575	7.87	<.0001
AR3	-0.2928	0.0639	-4.58	<.0001
AR12	-0.4037	0.0669	-6.03	<.0001

Graphical representation reinforces the numeric trends. Whilst the number of prescriptions continued to increase after the introduction of the NPI 2012 -2013, the rate of increase significantly slowed (Figure 6.4).

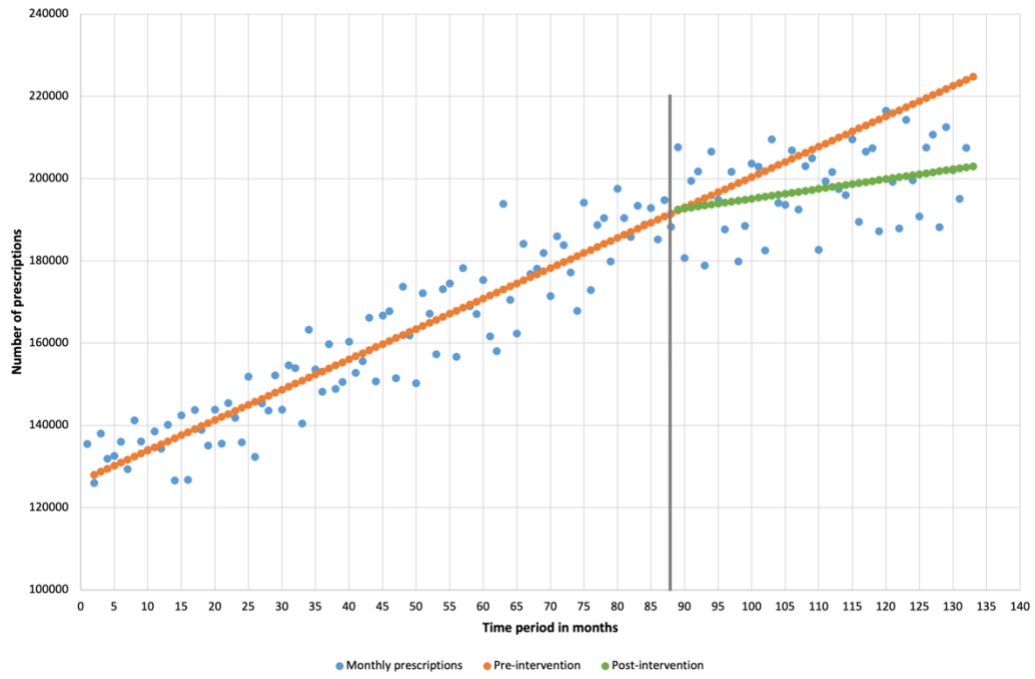


Figure 6.4: Plot of the number of opioid prescriptions between January 2005 (month 1) and December 2015 (month 132).
The solid grey line represents publication of National Prescribing Indicator 2012-13 which focussed on increasing the percentage of morphine as a total of all strong opioid prescribing

6.5.2.1 Weak opioids

Weak opioid prescribing was not the focus of the NPI 2012- 2013. However, following its introduction, the ITSA model demonstrated a non-significant step-

down in prescribing and a subsequent trend of reduction in the number of monthly prescriptions issued (Table 6.3).

Table 6.3: Results of interrupted time series analysis of weak opioid prescribing data

Parameter estimates				
Variable	**Estimate (95% CI)**	**Standard Error**	**t Value**	**Approx Pr > |t|**
Intercept ($ß_0$)	121148	1111	109.07	<.0001
Pre-intervention trend ($ß_1$)	569.8058 (528.62 – 610.99)	21.0116	27.12	<.0001
Change in level ($ß_2$)	-313.1082	1457	-0.21	0.8302
Post-intervention trend ($ß_3$)	-594.2796 (-705.29 - -483.27)	56.6371	-10.49	<.0001
AR1	0.4658	0.0570	8.17	<.0001
AR3	-0.2956	0.0632	-4.68	<.0001
AR12	-0.4102	0.0662	-6.20	<.0001

Graphical modelling of the ITSA reinforces the negative trend (Figure 6.5) noted in the number of weak opioid prescriptions issued each month in the study period following the intervention at month 88 (April 2012). The overall effect is to plateau the data for the remainder of the study period. This corroborates previous trends described in Chapter 3.

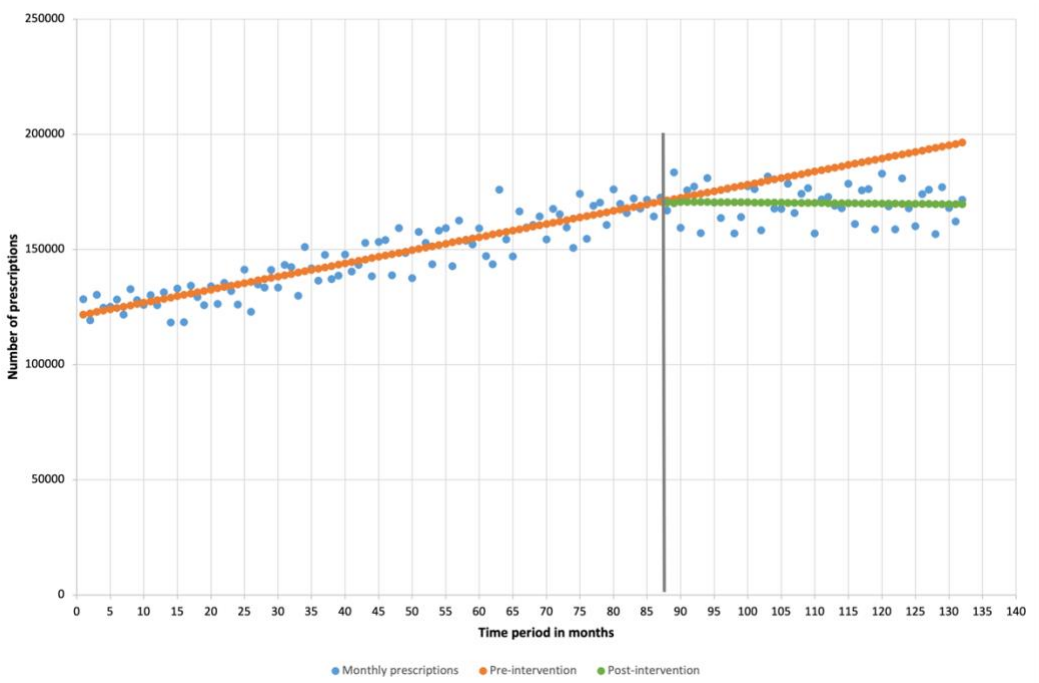


Figure 6.5: Plot of the number of weak opioid prescriptions between January 2005 (month 1) and December 2015 (month 132).
The solid grey line represents publication of National Prescribing Indicator 2012-13 which focussed on increasing the percentage of morphine as a total of all strong opioid prescribing

As with the overall trends, AR3 and AR12 values suggest seasonal variation (Table 6.3) but this does not appear to have affected the overall pattern of prescribing noted in the model.

6.5.2.2 Strong opioids

Strong opioid prescribing prior to the intervention demonstrates a significant positive trend based on the ITSA model used and in line with the data already discussed (Chapter 3 and Chapter 4). There was a non-significant step-up in the model, following the intervention as there was with the overall prescribing ITSA (Table 6.2), followed by a continued positive trend. However, the rate of increase appears reduced post-intervention based on the model output (Table 6.4).

Table 6.4: Results of interrupted time series analysis of strong opioid prescribing data

Parameter estimates				
Variable	**Estimate (95% CI)**	**Standard Error**	**t Value**	**Approx Pr > |t|**
Intercept ($ß_0$)	6253	453.8995	13.78	<.0001
Pre-intervention trend ($ß_1$)	170.1021 (152.11 – 188.09)	9.1780	18.53	<.0001
Change in level ($ß_2$)	430.7013	351.6284	1.22	0.2230
Post-intervention trend ($ß_3$)	112.3238 (74.74 -149.91)	19.1771	5.86	<.0001
AR1	0.1361	0.0694	1.96	0.0521
AR3	-0.3425	0.0676	-5.07	<.0001
AR12	-0.3479	0.0867	-4.01	<.0001

The trend post-intervention appears more rapid when depicted graphically (Figure 6.6). Previous trend analysis (Chapter 3) confirmed a slowing in annual percentage increase in the latter half of the study period which the ITSA model corroborates.

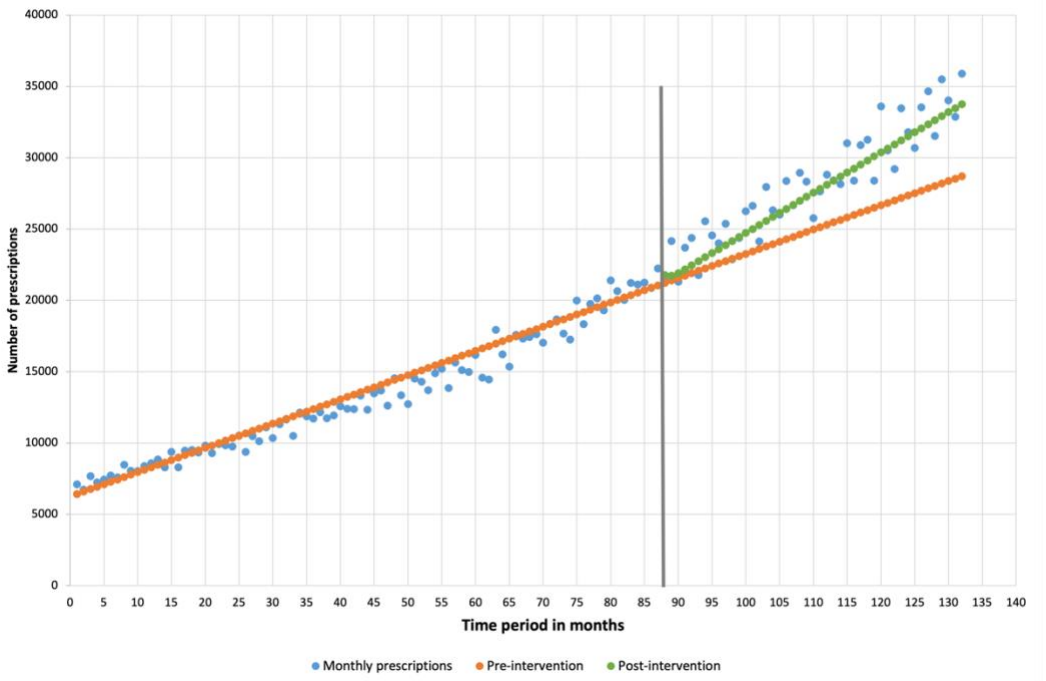


Figure 6.6: Plot of the number of strong opioid prescriptions between January 2005 (month 1) and December 2015 (month 132).
The solid grey line represents publication of National Prescribing Indicator 2012-13 which focussed on increasing the percentage of morphine as a total of all strong opioid prescribing

6.5.2.3 Changes examined by gender

ITSA by gender and examining all-type opioid prescribing clearly showed positive trends in monthly opioid prescriptions being issued prior to the intervention at month 88 (Table 6.5).

*Table 6.5: Output from Intermittent Time Series Analysis by gender (full data in **Error! Reference source not found.**)*

Estimate (95% CI)	Intercept ($ß_0$)	Pre-intervention trend ($ß_1$)	Change in level ($ß_2$)	Post-intervention trend ($ß_3$)
Men	47169	316.6277	573.3097	-224.7378
Women	80139	421.1498	186.3049	-275.5532

The model demonstrated the gradient for men was lower than for women, suggesting a slower rate of increase in monthly prescription numbers (Table 6.5).

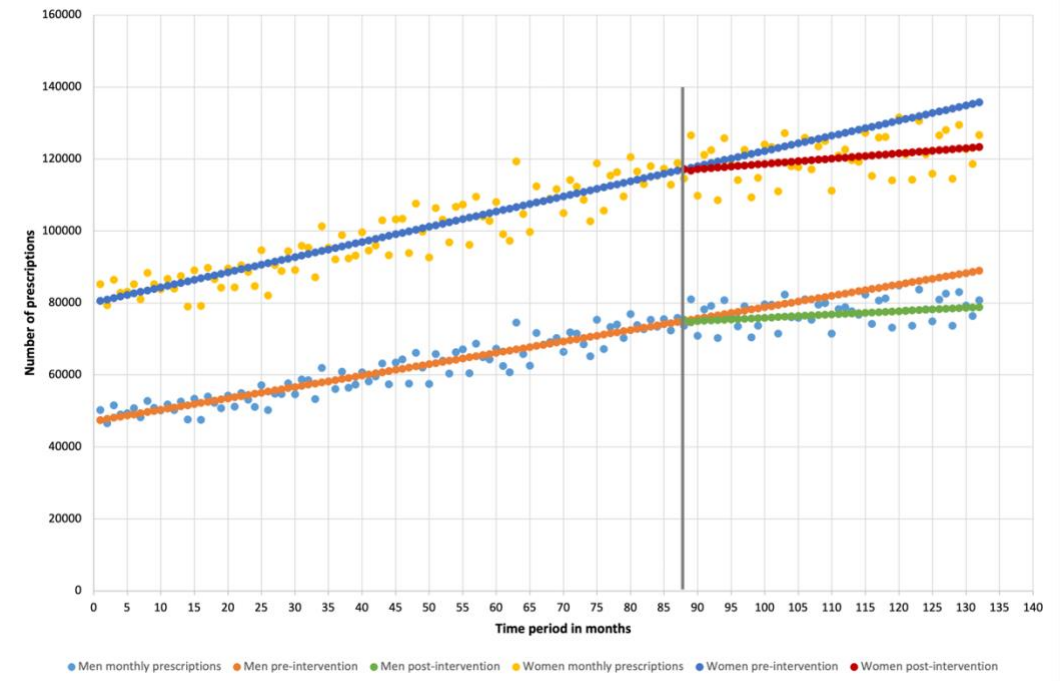


Figure 6.7: Plot of the number of opioid prescriptions issued by gender, between January 2005 (month 1) and December 2015 (month 132).
The black line is the intervention as previously described.

The intervention was followed by non-significant step-ups and then both genders were shown to have a reduction in overall numbers of prescriptions issued thereafter. As with previously described models (Section 6.5.2.1, Section 6.5.2.2 and Section 6.5.2.3) seasonal variation was demonstrated within both models but did not appear to influence the trends overall (Figure 6.7).

6.5.2.4 Changes by socioeconomic deprivation

ITSAs conducted for each socioeconomic deprivation quintile reinforced previously described differences between the most and least deprived areas (Section 4.5 and Section 5.5.4). All quintiles had positive trajectories prior to the 2012 intervention (Table 6.6).

Table 6.6: Output from Intermittent Time Series Analysis by socioeconomic deprivation quintile (full data in Appendix E)

Estimate	Intercept ($ß_0$)	Pre-intervention trend ($ß_1$)	Change in level ($ß_2$)	Post-intervention trend ($ß_3$)
WIMD1	37163	194.9836	418.1434	-135.0756
WIMD2	28836	167.1922	242.2058	-128.7473
WIMD3	24929	142.9455	189.2449	-92.1285
WIMD4	16719	118.6457	-140.2672	-87.9440
WIMD5	15083	95.1271	59.3972	-73.9886

Seasonal variation was detected, as with previous models, but again did not appear to influence the trends either pre- or post-intervention (Table 6.6).

Following the introduction of NPI 2012-2013, prescribing rates in all quintiles reduced, demonstrated by negative post-intervention trends.

6.5.2.5 Seasonal variation

Seasonal variation was observed throughout the year. The largest variation was seen between January, February and March (Table 6.7) but did not have an effect on the overall upward trend in prescription numbers over the study period.

Table 6.7: Average seasonal effects of opioid prescribing based on time series analysis and displayed by type of opioid prescribed

Month	Average seasonal effects		
	Total	Weak	Strong
January	2349.183	2348.167	1.016667
February	-11018.1	-9832.21	-1185.9
March	6107.283	5518.267	589.0167
April	-627.197	-606.97	-20.2273
May	-199.182	-165.235	-33.947
June	-1192.87	-939.5	-253.371
July	3358.129	2836.568	521.5606
August	-2008.03	-1831.77	-176.265
September	-292.341	-211.159	-81.1818
October	2915.683	2674.175	241.5083
November	-1593.24	-1365.79	-227.45
December	2502.383	1850.45	651.9333

The seasonal variation seen with weak opioid prescriptions mirrored the overall pattern (Figure 6.8), which was not unexpected given the proportion of weak opioids prescribed compared to strong opioid medicines. Strong opioid prescribing fluctuated in a similar vein to the overall trend, however, the degree of fluctuation was much less than seen for total and weak opioid data (Figure 6.8).

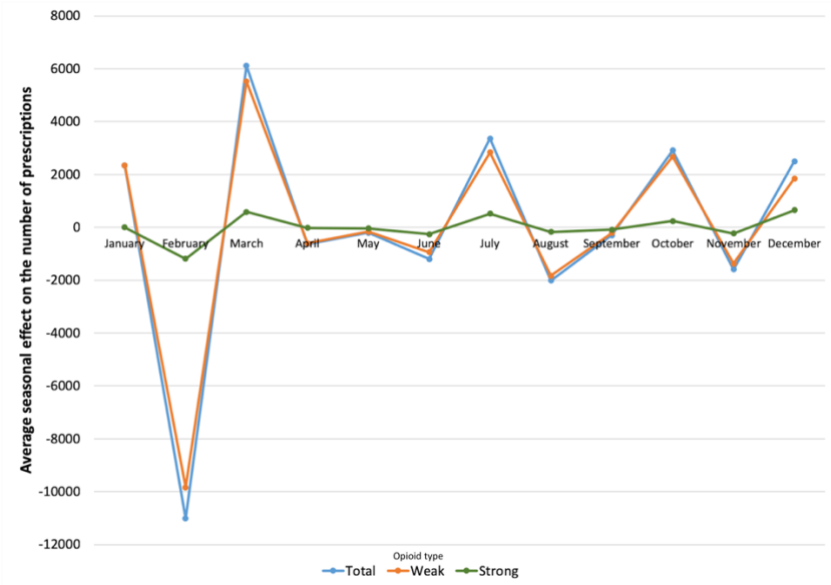


Figure 6.8: Graphical depiction of average seasonal variation in the number of opioid prescriptions, by type of opioid issued from time series analysis

6.5.3 Predictions

Predictions were made for the potential trends in future opioid prescribing with different models compared (Figure 6.9). Whilst all models had high coefficients of determination (Table 6.8), certain predictions appeared less likely from a clinical perspective. For example, the dramatic decline in prescribing predicted by the 3rd order polynomial trendline would seem an improbable outcome based on clinical experience. Similarly, the linear prediction would seem to be less reflective of the slowing in the number of annual prescriptions noted towards the end of the study period.

Table 6.8: Comparison of predicted trends in opioid prescribing using trendline analysis

	Polynomial			Linear
	x^2	x^3	x^4	
R^2	0.9882	0.9956	0.9963	0.9695
Predicted values				
January 2018	207067	185784	213668	232144
January 2020	219378	150439	215529	247242

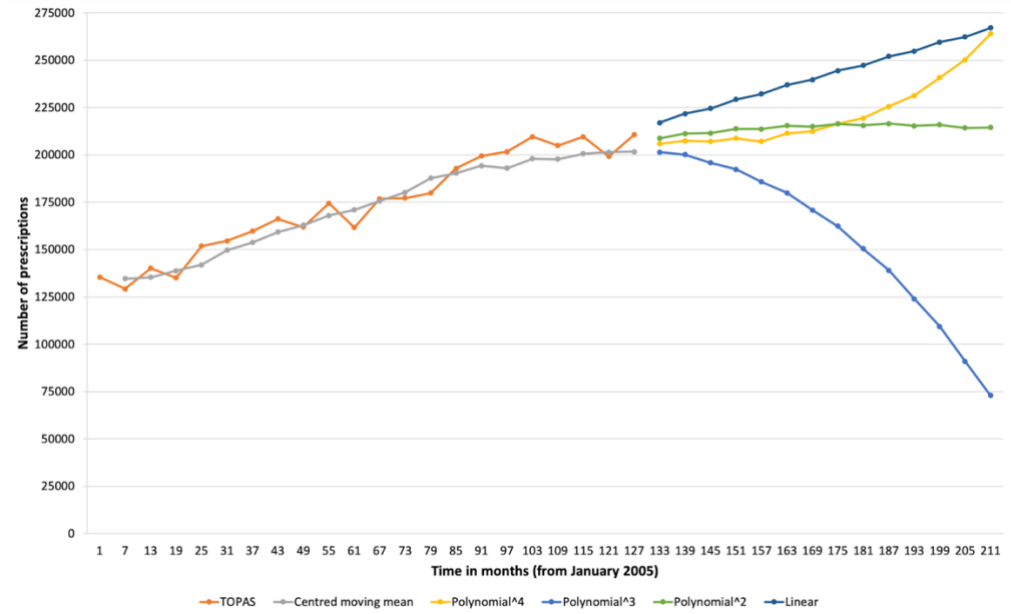


Figure 6.9: Predicted trends in the number of opioid prescriptions issued using different time-series trendline analysis

Predictions were made for all the TSAs conducted for this study. However, whilst the R^2 values indicated a high degree of accuracy for the predictions made, the trends themselves were made from non-stationary data and so predictive quality was likely to actually be low. The predictions for overall opioid prescribing, weak and strong opioid prescribing are provided in Figure 6.9 and the rest are presented in Appendix E.

6.6 Discussion

6.6.1 Summary and reflection on findings

Time series analysis reinforced the findings from the trend analyses reported in Chapter 3 by confirming the large increases in the number of prescriptions issued between 2005 and 2015. Fluctuations in prescribing followed a similar pattern and did not strongly correlate to a seasonal pattern, although seasonal variation was detected. However, fluctuations were much less marked for strong opioid prescribing. It appears the prescribing data was sufficiently accurate to predict the progress of prescribing during the eleven years of the study.

Less certain was the influence of changes in controlled drug prescribing legislation over the period examined. Whilst the rate of overall prescribing was starting to slow from around 2013, this does not appear to be linked to

legislative changes. The introduction of the NPI for 2012 – 2013, focusing on increasing the percentage of morphine prescribed as a proportion of all strong opioid prescribing does appear to have influenced prescribing. Although strong opioid prescribing continued to increase after the NPI was launched (Figure 6.6), the rate of increase was tempered. This could be a result of drawing attention to the concerns about rising opioid levels in general, or a concerted effort to avoid strong opioids where possible, despite the issue of NICE guidance which could be seen as encouraging opioid use for some common non-cancer conditions. Weak opioid prescribing demonstrated a reduction following the intervention (Figure 6.5). Why this would be the case following an NPI focused on strong opioids is not clear. Around this time, concern was growing about opioid associated deaths, especially those associated with tramadol, which was classed as a weak opioid for this study (Office for National Statistics 2020). It is possible this was an influence on choice of opioid.

Predicting future changes in prescribing, on the basis of what was observed before, proved unsatisfactory. Whilst the models used to predict forthcoming trends appeared reliable in terms of their R^2 values, a clinical 'sense-check' suggests some of the predictions would be extremely unlikely in practice. It is difficult to state with confidence whether TSA is a useful method of predicting future behaviour, not least as clinical decision making is an individual process which makes forecasting difficult (McIntosh et al. 2016; Murshid and Mohaidin 2017). Further, this analysis seems to illustrate more work is needed to find an effective method of implementing change, whether through guidelines or other means. Despite the introduction of legislation designed to improve patient safety and governance of prescribers, as well as guidance to affect prescribing choices, opioid prescribing continued to increase. Determining the 'buttons' that need to be pushed to get professionals on board with the changing evidence base will be essential if meaningful change in practice is to occur.

6.6.2 Is TSA a useful means of predicting prescribing trends or changes?

The most notable feature of the predictions made for opioid prescribing in Wales, from the TOPAS data, was their variance. It is more common to see TSA being used to compare actual versus predicted trends, rather than simply predicting forward, as attempted here. Helgason (2008) used TSA as a means of developing an algorithm for predicting drug selection based on prescribers' previous choices and combinations of medicines prescribed (Helgason 2008). The use of TSA in this instance was to reduce the time taken to choose medicines, as part of an electronic prescribing programme. There was up to 70% accuracy found in the predictions developed although it was noted that lack of data for less commonly prescribed medicines had the effect of reducing the reliability of the predictions (Helgason 2008).

Predicting the outcome of prescribing is difficult, due to the complex nature of pharmacokinetics and pharmacodynamics in each individual (Larney et al. 2018). For example, TSA combined with cluster analyses were shown to be helpful in predicting the response to pregabalin therapy in a group of patients with painful diabetic neuropathy, when compared to their real-time outcomes (Alexander et al. 2019). However, the model was not able to accurately predict which patients would develop adverse effects or discontinue treatment. Predictions, consequently, were binary, i.e., either someone would have a positive response or not (Alexander et al. 2019).

Studies examining the impact of legislation on prescribing trends have tended to use TSA as one part of the analysis (Gomes et al. 2014; Chang et al. 2016; Martin et al. 2018) suggesting the method may not have sufficient forecasting power on its own. The accuracy of predicting events declines the further into the future projections are attempted (Sherman et al. 2017). The complexity of decision making involved in prescribing decisions is difficult to account for in statistical modelling, as clinical decision making is rarely subject to only one or two static factors (Sherman et al. 2017).

What effective TSA studies have in common is access to a large volume of data (Härdle et al. 1997; Bernal et al. 2017). The TSA presented here evaluated more than 22 million data points over the study period, which assists the precision of the analysis. Accuracy of TSA improves with data volume (Bernal et al. 2017) . Using national data sources such as the SAIL databank, where large datasets are available, are therefore suited to time series analyses of trends (Falk et al. 2012; Bernal et al. 2017), provided the limitations of the method for clinical decision making are taken into account.

6.6.3 Effects of legislation on prescribing trends

It was somewhat surprising that changes in UK law (Dyer 2004) designed to strengthen the checks and safety of prescribing opioid medicines appeared to have little effect on overall prescribing rates observed in this study. Jani et al. (2020) made the same observation following a large study examining opioid prescribing trends in the UK between 1998 and 2016. A reduction in tramadol, oxycodone and fentanyl was observed in primary care prescribing from 2012 onwards (Jani et al. 2020), as it was in Wales. Jani et al. suggests this may have been related to national regulations introduced in 2013, although, as with TOPAS data, it did not appear to affect prescribing rates of all opioid analgesics equally (Jani et al. 2020). This appears to be in contrast to earlier reported findings outside of the UK (Gomes et al. 2014) where a noticeable reduction in opioid prescribing followed Canadian law changes that increased prescription monitoring. Conversely, legislation changes introduced in Italy, increasing access to opioids for a wider range of conditions and consequent growth in the number of prescriptions for strong opioids in particular, was noted (Musazzi et al. 2018).

Whilst the two studies had different outcomes, the legislation and monitoring put in place both had the desired outcome. In Italy, for example, prior to the freeing up of prescribing, there was concern that pain was being undertreated (Musazzi et al. 2018). The change in the law and reimbursement allowed opioid analgesics to be prescribed and dispensed in more healthcare sectors, seemingly reducing inequality in pain management (Musazzi et al. 2018). The fear in

Canada, however, was over-use and inappropriate prescribing of opioid analgesics, especially in the context of the opioid-crisis that was already hitting North America hard at that time (Dhalla et al. 2011; Gomes et al. 2014). The new legislation aimed to strengthen checks on prescribers and patients, by recording and monitoring who was issuing and receiving opioid analgesic prescriptions. Both interventions resulted in a reduction in prescribing (Gomes et al. 2014).

Legislation introduced in the UK over the years of this study was not focussed on the clinical use of opioid analgesics, unlike that in Italy and Canada during the same period (Gomes et al. 2014; Musazzi et al. 2018). Instead, their aim was to improve opioid analgesic prescribing and dispensing monitoring, enhanced record keeping and more clearly setting out how general practitioners in particular should be supervised and investigated in terms of concerns about their practice (Smith 2004; Department of Health 2013). Even when the Shipman inquiries (Section 1.11) were still fresh in the minds of practitioners, there was doubt how effective the new measures would be in preventing something similar again (Gallagher 2006). The over-riding aim of the changes was to prevent harm being caused to people subjected to opioid treatment and who were determined vulnerable on the basis of being frail or at the end of life (Dyer 2004; Baker 2004).

Relating this all back to prescribing trends in Wales, it seems reasonable to suggest that the limited effect of legislation might in part, be due to how it was implemented in practice. For example, changes to prescription writing requirements were mostly covered by general practice prescribing software (National Institute for Health and Care Excellence 2016). The more stringent documentation that pharmacists are required to complete and maintain (Royal Pharmaceutical Society of Great Britain 2021) has little impact on prescribers themselves, unless they are part of a dispensing practice. Perhaps changes in practice are more likely when prescribing becomes more inconvenient to the prescriber?

The response to the opioid crisis in North America and the USA in particular, has been to impose and enforce fairly draconian laws and payment restrictions on prescribers (Ayres and Jalal 2018; Martin et al. 2018; Schatman and Shapiro 2019). Such changes have resulted in the sudden cessation of opioid prescriptions for thousands of people (Mundkur et al. 2017; Singer et al. 2019). Commentators have suggested such strict measures are directly responsible for people seeking out illicit opioids through cryptomarkets (Martin et al. 2018; Mundkur et al. 2018) and direct sales. Others have suggested stable prescribing rates, in tandem with rising synthetic opioid (fentanyl and diamorphine/heroin) deaths point more towards rising rates of illicit opioid use, rather than a problem of over-prescription (Singer et al. 2019). High rates of overdose-related deaths are still being seen in the USA, with 49,860 opioid associated deaths reported in 2019 (Centers for Disease Control and Prevention 2021).

6.6.4 Abolition of prescription charges

Prescription charges were abolished by the Welsh National Assembly Government in 2007, as a means of improving chronic condition management. The change did not appear to have a direct effect on the rate of opioid prescribing, based on the analysis. This confirms the findings of the (then) Welsh National Assembly Government who conducted a review of the changes 3 years after their introduction (National Assembly Government 2010). Prior to the removal of charges, 88% of all prescription items were dispensed without charge in Wales (National Assembly Government 2010). Consequently, the change is likely to have affected only a small proportion of prescribing and more likely to have been in the more affluent areas of Wales, where overall opioid prescribing levels were lower.

6.6.5 Effects of national prescribing indicators and guidelines on prescribing trends

On the basis of the interrupted-TSA conducted, there was some, albeit limited, influence of NPIs on overall opioid prescribing trends between 2005 and 2015. This contrasts with findings from an earlier study which found non-steroidal anti-

inflammatory prescribing was influenced by the introduction of NICE guidelines for osteoarthritis (Bedson et al. 2013). The same study noted that the advice not to prescribe and subsequent withdrawal of co-proxamol, from the UK market in 2005 on safety grounds, led to a substantial reduction in its use (Bedson et al. 2013) (Appendix D). However, being unable to access a medicine is different to advising against its use whilst it remains available. The rapid reduction in co-proxamol use in Wales and the UK in general, was aided by not being able to order it and its cost subsequently becoming prohibitive. This has not been the case with other opioids. As these TSA's demonstrate, whilst co-proxamol reduced in Wales, it was rapidly replaced and superseded by other analgesics. It may be hypothesised that the message around opioid safety was perhaps viewed as being a concern for co-proxamol but not extrapolated in the minds of prescribers much farther, given no indication of changes in prescribing rates were detected until 2012.

NICE guidance for osteoarthritis issued in 2008 did not make clear recommendations for or against the use of opioid analgesics (National Collaborating Centre for Chronic Conditions 2008). The 2009 guidance for persistent low back pain specifically recommended the short-term use of strong opioids (National Institute for Health and Clinical Excellence 2008). However, they did not provide information on monitoring effectiveness or stopping opioid analgesics, which were not of benefit. The TSA did not examine data by duration of prescribing, so it was not confirmed if the increase was in part due to more short-term prescriptions. However, the rise in prescribing noted up until 2012, was underway prior to the publishing of the NICE guidelines. Whilst analgesic related NPIs were in force throughout the study period, those related to opioids specifically, were not introduced until the 2012 to 2013 financial year (All Wales Medicines Strategy Group 2013). There was a slowing in the rate of increase after 2012, but it is not clear if it was stimulated by the NPIs themselves. Taking the results from all the trend analyses conducted for TOPAS (Chapter 3, Chapter 4 and Appendix E), a more nuanced picture emerges. Annual tramadol prescribing began to reduce between 2013 and 2014, although the NPI aimed at

reducing tramadol prescribing introduced in response to a marked increase in tramadol-related deaths in Wales was not launched until the 2014 to 2015 financial year (All Wales Medicines Strategy Group 2013; Welsh Analytical Prescribing Support Unit 2013). Morphine was the most frequently prescribed strong opioid in Wales throughout the study period (Appendix D). Prescribing increased annually between 2005 and 2015 and whilst the rate of increase by prescriptions per 1,000 population did not change following the NPIs introduction, the oral morphine equivalent dose did rise towards the latter part of the study (Appendix D). The implication of this finding may be that prescribers felt confident to prescribe higher doses, as well as to more people. This was not likely to have been the hope of those who developed the indicator.

Neither Welsh NPIs nor NICE clinical guidelines have a legal basis and so are reliant on local arrangements, in terms of any enforcement, which may account for their varied impact on opioid prescribing and clinical practice. In contrast, regulatory standards and guidelines introduced to British Columbia, Canada in 2016, led to an average reduction of 57mg oral morphine equivalent (OMEQ) per month in overall prescribing and reduced dosing for people receiving long-term prescriptions (Morrow et al. 2019). Similar reductions have been noted where prescription monitoring systems, which allow prescribers to see if patients are accessing prescriptions from other sources, have been implemented (Gomes et al. 2014; Chang et al. 2016). Legal enforcement of national guidance (Dowell et al. 2016) has also been used to address rising overdose deaths in the USA, where prescription opioids and the prescribers have been implicated (Weisberg and Stannard 2013; Coyle et al. 2018). Consequently, overall rates of prescribing in the USA have reduced by over 40% (from 81.3 to 46.7 prescriptions per 100 people) between 2012 and 2019. Reductions have not been seen in all areas, however. More rural areas or areas with higher levels of socioeconomic deprivation, continue to report prescribing rate six times higher than the average (Centers for Disease Control and Prevention 2021).

Although, NPIs are used to benchmark prescribing trends, there is not an available measure for assessing whether analgesic prescribing complies with clinical guidelines from NICE or elsewhere.

6.7 Conclusion

Time series analysis is a useful method of determining the influence of changes in prescribing. Using TSA as a lone means of predicting future events has limitations but may be helpful in combination with other analyses. Reviewing how effective previous guidelines or legislative changes are in securing practice transformation should be seen as an essential part of developing new ones. Understanding the factors which combine to promote change should help cultivate more effective methods of supporting meaningful modifications in future.

Whilst modest, the changes in tramadol prescribing in Wales most closely echo other successful combinations of legislation changes, education and prescribing guidance elsewhere (Gomes et al. 2014; Chang et al. 2016; Musazzi et al. 2018). The combination of efforts likely increased the attention paid to the problem and therefore, acted as an encouragement and reminder for change. Similar influences were not used in Wales for other opioid-related prescribing issues however, and this may be why there was little effect on opioid prescribing overall.

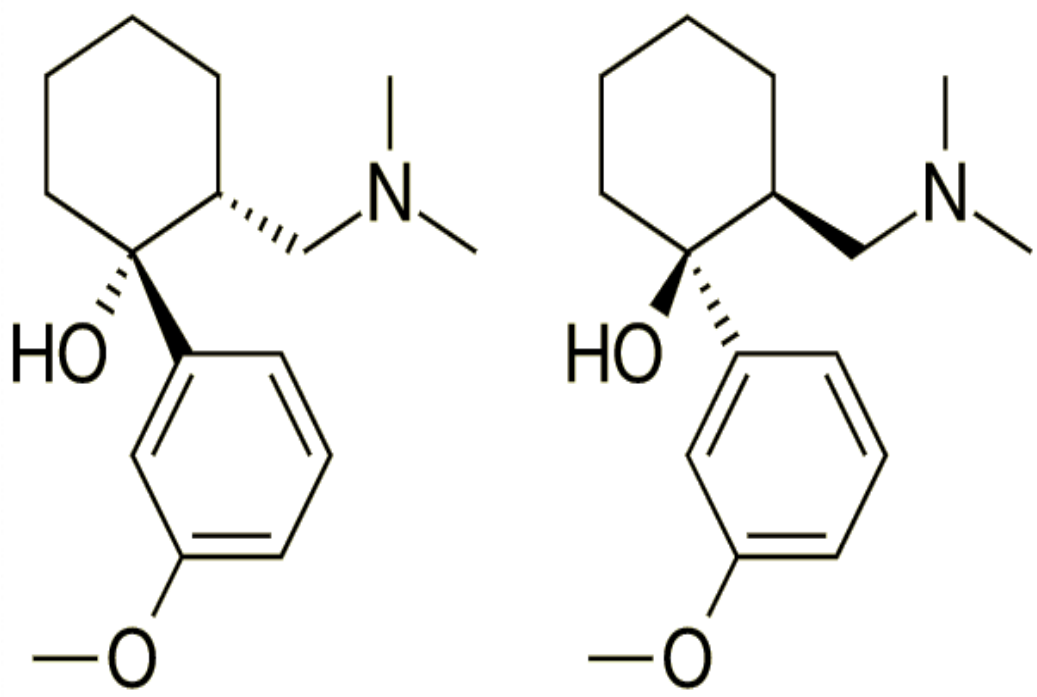
Devising and introducing new legislation to control, or direct prescribing might be necessary to demonstrate a commitment to patient safety. However, using examples where it has led to a positive change (Gomes et al. 2014; Chang et al. 2016; Fink et al. 2018; Welsh Government 2019), it appears law changes may be best introduced in combination with clinical guidelines or other forms of monitoring that more noticeably affect daily practice. Regardless of the method adopted to improve prescribing, whether it is guidance or legislation, implementation is key. Examining methods for improving the uptake and

compliance with prescribing recommendations and monitoring prescribers compliance with them would be a useful piece of further research.

Phase 2

Chapter 7

Healthcare resource utilisation associated with opioid prescribing and associated cost-analysis



"It doesn't matter how many resources you have. If you don't know how to use them, it will never be enough."
Anon

Chapter 7 - Healthcare resource utilisation and cost-analysis associated with opioid prescribing

7.1 Chapter overview

Phase 1 of the study reviewed the socioeconomic burden of pain and the use of opioid analgesics as part of its management. The results presented in Chapters 3 and 4 demonstrated large increases in the prescribing of all opioids in the 11 years examined, with women and older people receiving greater numbers of prescriptions. Prescribing in areas of greatest socioeconomic deprivation is much higher than in more affluent areas. Further, as set out in Chapter 5, marked increases in strong opioid prescriptions, added a disproportionate burden in oral morphine equivalent terms, in comparison to weak opioids. More people were receiving opioid prescriptions for longer periods of time by the end of the study duration, based on prescribing persistence data. As discussed in Chapter 6, the introduction of controlled drug legislation and to some extent NPIs in Wales, only limitedly tempered the rising rates of prescribing.

Phase 2 of the study now examines the combined effect of the trends reported so far, insomuch as it examines the impact of opioid prescribing on healthcare utilisation in Wales. For the duration each person received opioid prescriptions, their attendance at healthcare services in primary and secondary care were counted and compared to people with similar conditions but not receiving opioid prescriptions. A healthcare service-based cost-analysis was undertaken to provide an estimation of the potential impact of opioid analgesic use on healthcare budgets.

7.2 Study objectives to be addressed in this chapter

- To assess the frequency of primary and secondary healthcare attendance by patients with defined non-cancer pain conditions receiving opioid analgesic therapy
- To estimate healthcare service costs associated with the use of opioid analgesics

7.3 Background

As time goes on, an increasing number of treatments, for a wider range of health conditions have become available. Simultaneously, people expect, and demand more say in what they want to receive in terms of healthcare. However, there will never be enough resources for everyone to have everything they want. This applies to healthcare as much as it applies in life.

7.3.1 Efficiency

Health economics attempts to maximise the output from a limited input. Two concepts, efficiency and equity form the central themes of health economic analysis (Phillips 2005). The most efficient system is one where changing the use of resources would not result in more benefit than is already being achieved. The implication is that all available resource is being used optimally and any reallocation, would require something to be given up elsewhere in the system (Phillips 2005). This phenomenon is also known as Pareto equilibrium (Kaplow and Shavell 2001) and could be argued is perhaps aspirational, rather than achievable in modern healthcare.

Efficiency can be derived in several ways. The NHS would appear to aim for efficiency saving most of the time. Commonly referred to as cost-effectiveness, the goal is to produce the same output for less money or to use the available resources to provide more services or treatments (Phillips and Thompson 2009). The reality, however, is that it is increasingly difficult to provide more without someone, somewhere losing out. Claxton et al. (2015) discussed this issue in relation to NICE changing its limits for cost-effectiveness of new therapies (Claxton et al. 2015). Claxton et al. suggested that, over time, the threshold for the acceptable cost per quality- adjusted life-year (QALY) considered by NICE had crept up. The maximum, previously considered to be a reasonable balance for healthcare services and society to bear, had in fact, become the minimum. It was postulated that the reason this had been allowed to happen, was due to the

absence of those who truly bear the opportunity cost of the decision in decision-making processes (Claxton et al. 2015).

7.3.2 Welfarism

Welfare in economic terms can also be referred to as 'well-being'. Societal improvement is most likely to occur when an individual or organisation improves their own well-being, without that improvement being at the expense of another (Coast et al. 2008). Welfarism in health economic terms includes the notion that healthcare outcomes should be judged by their contribution to an individual's overall well-being (Brouwer et al. 2008; Coast et al. 2008). Positive health outcomes might be seen as equally important to good educational outcomes for example. Welfare theory would suggest therefore, that treating a person who manages their health condition and is able to generate good personal utility (well-being), is not an efficient use of resource. Instead, it is deemed more efficient to treat people who cope poorly with their health and whose utility is less. Cost-benefit analysis is used to aid welfare-based decisions (Kaplow and Shavell 2001; Shafrin 2008).

7.3.3 Extra-welfarism

Extra-welfarism centres on cost-effectiveness analysis. The theoretical basis of extra-welfarism assumes that people with the same condition value their health equally (Coast et al. 2008). Cost-effectiveness compares the cost and outcome of different interventions to determine which provides best value for money (The What is …? series. 2014). Outcome measures in this approach are focused on health only and do not draw in non-health related utility (i.e., a treatment reduces reported pain intensity but there is not a measure of whether people are able to return to work). Extra-welfarism may also look to illicit a measure of willingness to pay from those who are providing or receiving the health intervention under examination (Gyrd-Hansen 2005). This is where the theory comes under strain as it is difficult to be assured a whole population values health equally (Gyrd-Hansen 2005; Brouwer et al. 2008; Bobinac et al. 2010).

7.3.4 What approach do we take to Heath Economic Analysis in Wales and the UK?

In truth, there is no perfect approach to Health Economic Analysis (HEA). Nuance exists in every system, and it can be hard to measure outcomes across health and social care systems if data is not collected or available for analysis. On a theoretical basis, welfarism is often considered to be the preferable approach to decision making (Brouwer et al. 2008; Coast et al. 2008). Certainly, it seems sensible to view outcomes across a range of services and systems to truly understand their benefit. In reality however, it is not always realistic to pursue a welfarist approach in practice. Health economists are pragmatic and therefore, a range of measures are utilized, including cost-effectiveness (Coast et al. 2008).

7.3.5 Equity and equality

Equity differs from equality, insofar as it is based on need rather than giving all people the same. The International Monetary Fund (IMF), whilst not directly concerned with healthcare, have stated equity is '*a worthy goal in and of itself because of its moral implication and its intimate link with fairness and social justice'* (Expenditure Policy Division et al. 1998). Twenty years ago, when the need for equity in economic policy was being discussed, it was proposed that when equity is promoted, poverty is reduced and vice versa (Expenditure Policy Division et al. 1998; Braveman and Gruskin 2003). Braveman and Gruskin (2003) proposed health equity reduced the 'unequal opportunities to be healthy' commonly associated with being poor, disenfranchised racially, ethnically or religiously, being female or residing in rural locations (Braveman and Gruskin 2003). A welfare approach to healthcare could therefore be seen as the most equitable.

7.3.6 Use of healthcare services

It is accepted that people living with painful conditions access more healthcare resources than those without (Mehra et al. 2011; Bozic et al. 2012). Pain is often considered to be a symptom of an underlying condition; although increasingly, it

can be considered as a condition in its own right (Raffaeli and Arnaudo 2017; Treede et al. 2019; National Institute for Health and Care Excellence 2021). People living with chronic pain especially, tend to have multiple co-morbidities (Macfarlane et al. 2020). For example, nearly 60% of people with neuropathic pain conditions were noted to have more than four co-morbid conditions (Berger et al. 2012). Conversely, over a third of people receiving at least one weak or strong opioid in a study of one year, did not have a defined diagnosis (Foy et al. 2016). Consequently, it can be difficult to determine whether reported healthcare use is linked to pain or another condition, unless specifically examined in the study.

7.4 Method

7.4.1 Study design

This phase of the study was designed as a retrospective, longitudinal case-controlled study that examined data from people aged 18 years and over and who did not have a recorded diagnosis of cancer at any time between 2004 and 2015 on their Primary Care General Practice medical record.

7.4.2 Cohort identification

The cohort for Phase 2 were identified initially from the WLGP event database. ALFs for individuals with read-codes for at least one of six over-arching chronic pain diagnoses, namely back pain, neck pain, osteo or rheumatoid arthritis, fibromyalgia and neuropathic pain (Appendix F), on their Primary Care medical record were used to trace their interactions with other healthcare services through the previously discussed data linkage processes used by SAIL (Chapter 2).

7.4.2.1 Case Subject group

Case subjects were identified by having an opioid prescription issued within the study period (2005 to 2015) . They were further stratified by the prescribing persistence (from less than 6 months up to 11 years) (Section 3.4.2.2 and Appendix F).

7.4.2.2 Control subject group

SAIL analysts specified the method for creating the control-group, based on the criteria provided in the research protocol (Appendix A) and using methodology previously used by that organisation (Akbari and Torabi 2017). The control group was composed of people who had a recorded diagnosis of one of the six chronic pain diagnoses but no record of receiving an opioid within the time period they were controlled against the subject group.

Controls were matched to case subjects by age within the age-groups previously defined (Section 2.6.4), gender, WIMD, and availability of medical records in the period between 2005 and 2015. Medical records for control subjects were matched to case subjects for the duration (years) that the case subject received prescriptions for opioid analgesics.

Control subjects were matched to multiple case subjects based on the criteria described. For example, if a control subject had 6 years of medical records without receiving an opioid prescription, they could be matched to case subjects who had received prescriptions for any period up to 6 years. This method of matching, analysis allowed four controls for each case subject in the cohort study but also resulted in each control being used up to 20 times.

Healthcare service utilisation was measured for the duration each case subject was in receipt of opioid analgesic prescriptions. Control subject healthcare service use was measured for the same time duration as the case subjects to which they were matched.

7.5 Data source

As per the first study phase, split files were used to transfer person level data into the SAIL databank. The Phase 2 data sources comprised:

- Welsh Demographic Service Dataset (WDSD) which maintains a register of demographic detail for every Welsh resident who is registered with a Welsh

GP practice. Information includes name, address, date of birth, GP practice and NHS number (Observatory 2020b).

- Welsh Longitudinal General Practice (WLGP) data (GP event data) which is extracted directly using Audit+, from the electronic health records maintained by each GP practice in Wales. Includes appointments and contacts between the practice and patient, symptoms, test results, diagnoses, and prescribed treatment (Secure Anonymised Information Linkage Databank 2021).
- Annual District Death Extract (ADDE) is taken directly from the Office for National Statistics' register of all deaths relating to people residing in Wales, even if their death occurred outside of the country (Secure Anonymised Information Linkage Databank 2021).
- Patient Episode Database Wales (PEDW) which can provide a record of all in-patient and day-case hospital activity. From this database, it is possible to extract admission and discharge dates, length of stay (LoS), diagnoses, operative and investigative procedures undertaken as well as outcome data such as discharge destination (Secure Anonymised Information Linkage Databank 2021).
- Emergency Department data which provides date of attendance, method of arrival (e.g., walk-in, ambulance, etc.), injury and accident details and whether the person is admitted to hospital from the emergency room. Data is collected and coded at each hospital, extracted, and initially encrypted by the NHS Wales Informatics Service (Secure Anonymised Information Linkage Databank 2021).
- Outpatient data which can provide dates of attendance, whether it was a first or repeat attendance and which specialty the person was attending to see. Data is extracted from NHS Wales Informatics Service who, in turn, use data collected and coded at each hospital in Wales through the Patient Administrative System (Secure Anonymised Information Linkage Databank 2021).

7.5.1 Data identification

Data extraction specification was requested based on the study protocol (Appendix A). Read-codes (NHS Digital 2015) for prescribable opioid preparations were the same as for Phase 1 of the study. Identification codes for in-patient specialties were taken from the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10), used internationally and defined by the World Health Organisation. Codes were also taken from the Systemised Nomenclature of Medicine – Clinical Terms (SNOMED-CT), an international standardized vocabulary of clinical terms used throughout the National Health Service for collecting activity and intervention data (NHS Digital 2021).

Extensive lists of codes for diagnoses, tests, investigations, adverse events (ADE), specialty referrals, admissions and procedures were developed from the Clinical Terminology Browser, SNOMED-CT, and the ICD-10 lists. However, due to constraints in extraction capacity within SAIL, detailed analysis was deemed unfeasible. Consequently, extensive code lists for diagnoses, tests and investigations had to be reduced to a concise list of overarching title codes for referral to secondary care, blood tests and imaging (Appendix F). This resulted in far fewer 'flags' for these items within the extracted dataset than would be expected for the number of subjects included. Analysis was still performed but with caveats applied.

Demographic data collated for each study individual included gender, age, and deprivation data (WIMD2011), using the anonymised linkage systems of SAIL (Chapter 2).

The data was subjected to repeated cross-sectional sampling to determine the number of highlighted events in all relevant Healthcare sectors. Costings were applied to all units of healthcare utilisation that could be attributed from the extracted data.

7.6 Cost Analysis

7.6.1 Costs included in the analysis

The analysis of total healthcare costs associated with opioid use included:

- Costs of primary care general practice attendances (including staff time, tests, investigations, and imaging that resulted from appointment, where recorded)
- Costs of emergency department and out-patient attendances
- Costs of in-patient attendances including day/night costs and excess day charges

Insufficient data was available to allow costing of medicines or productivity losses. Furthermore, no quality-of-life data was recorded. Data regarding interventions made during attendance in any sector and detail of whether hospital admission was planned or unplanned could not be extracted from SAIL. Consequently, weighted average costs were assigned for each type of attendance.

Costs are expressed as 2014/15 UK pound sterling (£), which avoided the need to calculate inflation over the study period. Costs were not discounted as the data analysed was historical and a period of follow-up after the study end was not included.

7.6.2 Cost of healthcare resource use

Healthcare resource use, including Primary Care General Practice consultations, emergency department and out-patient attendances and in-patient stays, were collated from the different datasets available within the SAIL databank. Due to limitations in coding, only tests, investigations and imaging recorded using core codes (overarching codes for e.g., referral) were flagged. Consequently, this limited the number of people for whom those applied, although it applied equally to case and control.

Each anonymised individual, linked by the methods previously described (Chapter 2), was traced and every recorded attendance at any healthcare service 'flagged'. A final count for each of those attendances was included in a data table which had one line per individual. In-patient stays were recorded in more detail on a second table. This provided data on the admitting and discharging specialty, but interventions made during each admission were not recorded.

For Primary Care practice attendance, an average, weighted cost based on General Practitioner and Nursing costs (Curtis and Burns 2015) was calculated (Table 7.1). Weighting was based on published data which attributed 66% of Primary Care consultations to GPs or allied health professionals and 34% to nurses (Hippisley-Cox and Vinogradova 2009). Further, costs for investigations, blood tests, pathology and imaging were weighted and then averaged, based on the data available from National Schedules (Department of Health and Social Care 2015; Curtis and Burns 2015) (Appendix F).

Table 7.1: Unit costs for calculating Healthcare utilisation

Healthcare Unit	Unit Cost (£)	Notes
Primary Care		
General Practitioner	45.00	Includes allied health professional costing
Primary Care Nurse	14.00	Based on 15.5 minutes per appointment, 60 appointment per week, £45 (£56) per hour
Weighted Primary Care appointment	**34.46**	Based on 66% GP, 34% nursing time
Tests and investigations	**4.84**	Weighted by recorded numbers of blood tests, biochemistry and pathology, phlebotomy, and imaging
Imaging	**87.20**	Imaging data provided in addition to all investigations. Not included in total tests and investigations costings
Secondary Care		
Out-patient appointment	**110.04**	National costings give same cost for consultant-led and non-Consultant led appointments
Emergency Department attendance	**131.92**	Includes basic investigations
Day case acute care attendance	**707.61**	Includes minor operations, radiological interventions, administration of chemotherapy etc.
Elective In-patient admission	673.56	Based on £3641.24 for a weighted average 5.4 days admission
Elective in-patient admission excess days	342.64	For every day of an admission ≥ 6 days
Non-elective/unplanned in-patient admission	353.20	Based on £2969.07 for weighted average 8.4 days average excess days admission
Non-elective in-patient excess days	287.13	For every day of an admission ≥ 9 days
Weighted combined in-patient admission	522.99	Based on weighting from Welsh Providers 53% elective admissions, 47% non-elective admissions

Weighted combined in-patient excess days	316.55	
In-patient day/night costs	57.86	Applied to all admissions, based on £347.93 for a weighted average 6 days. Administrative cost of admission.
Total weighted in-patient admission	**580.86**	Weighted average cost for first 5 days of admission
Total weighted in-patient excess days admission	**374.42**	Weighted average cost for each day ≥ 6 days admission

(Curtis and Burns 2015). Example of more detailed unit costs in Appendix F. Unit cost = cost per GP visit, per test, per OPD or ED attendance or IP admission per day

Secondary care costs, emergency department and out-patient attendances and in-patient stays were calculated from National Schedules for 2014-15 (Table 7.1) (Department of Health and Social Care 2015; Curtis and Burns 2015). All costs associated with paediatric services were removed from the costings lists. Weighted out-patient, day-case, in-patient and excess in-patient costs were calculated from the unit costs provided (Appendix F for example of weighting calculation). Data from Welsh Providers was used to calculate a weighting for elective and non-elective admissions (53% versus 47% respectively) (Digital Health and Care Wales 2021), as this information was not made available in the data tables from SAIL.

Costs were assigned to each individual based on the total number of attendances for Primary Care or out-patient appointments. In-patient stay was provided by number of days. The national schedule was based on an average stay of 5.4 days. Consequently, in-patient stays between one and five days were costed at the weighted average (elective and non-elective) for standard in-patient days (allocated on a daily basis). If an in-patient admission continued for 6 or more days, any days over the first 5, were classed as 'excess days' and the weighted average excess days cost was allocated. Total in-patient costs were, consequently, the combined total of standard and excess days.

Any secondary care admission of less than one full day, where admission and discharge date were the same, were classed and costed as a day case and the weighted day-case cost used.

7.7 Statistical analysis

All statistical analysis was undertaken using SPSS version 26 (IBM Corporation 2021). Descriptive statistics, mean values, standard deviation, and standard error, were used to compare case and control groups.

Central limit theorem suggests when sample size is large, distribution tends to normal even if the population itself is not normally distributed (Lumley et al. 2002). Due to the large sample size in both arms of the study (case and control), it was determined parametric tests could provide accurate analysis.

To ensure the decision to adopt central limit theorem did not affect the analysis, non-parametric tests (Mann-Whitney and Kruskal-Wallis as per Chapter 2) were also performed between each factor, to compare cases and controls (Appendix F).

7.7.1 Student's t-test

Student's t-tests are used to contrast the means of two samples of normally distributed data (Field 2014). It works to a null hypothesis there is no difference between the groups being compared. Where differences are detected, the p-value provides an indication of whether they are due to chance or not, so a p-value of .05 means there is a 5% chance the difference between groups occurred by chance, or that out of 100 repetitions of the same situation or experiment, the result would be replicated 95 times. For this study, they were used to assess the magnitude of difference between healthcare utilisation and costs.

7.7.2 One-way analysis of variance (ANOVA)

One-way ANOVA is used to compare the means of two or more groups of data, although most commonly for three or more. The analysis tests the null hypothesis that all three (or more) groups have the same mean value i.e., the groups are not different to each other. For this study, one-way ANOVA was used in Chapter 7 to analyse differences in healthcare utilisation within e.g., case subjects stratified into 6 groups, depending on age.

7.7.3 Two-way ANOVA

A two-way ANOVA is used to test whether there is an interaction between two categorical variables (e.g., male or female), that combine to affect a dependent variable, or the outcome being examined. In this study, two-way ANOVA was used as a preliminary check of for example, whether receipt of opioid prescriptions had a greater effect on attendance in primary care for women than for men. The interaction effect between factors was deemed significant at a level of 5%. Where the interaction term was not significant, univariate tests (t-test or one-way ANOVA) were also conducted, in order to take account of the relationship and provide a more accurate comparison. For independent t-tests, Levene's test for equality of variance was checked and if significant (at 5%), unequal variance was assumed. Comparison of means using t-tests and one-way ANOVA also had a 5% significance level.

Two-way ANOVA was used to examine the interactions between gender, age-group, and socioeconomic deprivation (WIMD2011) (Appendix F).

7.7.4 Multiple linear regression

Regression analyses study the form and direction of the relationship between two or more variables. Regression analysis enables prediction of the value of one variable or the 'outcome' e.g., number of attendances in primary care, based on the values of other variables or 'predictors' e.g., gender, deprivation, age (Laerd Statistics 2021).

Regression analysis uses observations (data) to predict and quantify the relationship between a 'dependent' variable e.g., an outcome such as 'prescription for a strong opioid' and one or more 'independent' variables e.g., gender, age, deprivation status.

The basic equation for linear regression is

$y_i = (b_0 + b_1X_i) + e_i$

where y_i is the outcome being predicted; X is the predictor variable i.e. the independent variable being used to make the prediction of outcome; b_1 is a parameter which quantifies the relationship between the predictor and outcomes variables; b_0 is the parameter that provides the outcome variable when the predictor is zero and e_I is the error associated with the calculation (Field 2014).

In the case of this study, an example regression might be:

Number of prescriptions = b_0 + (b_1 x male gender) + ei

If the value of b_1 is negative, it would imply the variable e.g., male gender, had a negative effect on the outcome being predicted i.e., makes the outcome less likely.

In clinical situations, it is unlikely that any one factor on its own, will account entirely for the outcome of interest. In these situations, the use of multiple regression allows prediction of how different variables might affect the outcome of interest. Multiple linear regressions were performed to investigate whether there were relationships between healthcare utilisation and opioid use (including duration of use for those who received them), age, deprivation status and gender. Regressions were run with different predictors to determine the model which provided the 'best fit' or highest R and R^2 values. A higher R or R^2 value provides an indication of the accuracy of the model in making the predictions.

The equation for a multiple regression model is:

$$y_i = (b_0 + b_1X_i + b_2X_{2i} + b_3X_{3i} + b_4X_{4i} + b_nX_n) + e_i$$

where b_n is the coefficient for the predictor variable X_n i.e., as many variables as are of interest could be added. However, it does not always follow that more variables added in, lead to a better model.

7.7.5 Bonferroni-Holm correction

In any statistical hypothesis testing, there is a risk of mistakenly accepting errors. In simple terms, the null hypothesis states that any difference between comparator groups is due to chance rather than the effect of the intervention being tested. In most situations, efforts to reduce the risk of type-1 errors include setting the significance level at either 5% or 1% (p-values of <.05 or <.01). If those levels are met, it can be concluded the likelihood that the difference between groups is only 1-5% due to chance.

Type-1 errors are often referred to as 'false-positives'. The error results in the rejection of the null hypothesis when it should have been accepted. An alternative explanation is that a type-1 error will lead to a conclusion that a statistically significant difference exists between comparators when it does not. Conversely, failing to reject a false null hypothesis or accepting a 'false negative' is a type-2 error. In this case, it would be concluded that no statistically significant difference existed between comparators, when in truth, there was.

Claiming a chance difference as the outcome of an experimental intervention has potentially problematic implications. For this reason, type-1 errors are considered a risk that must be minimised. A potential risk for introducing type-1 errors occurs when multiple comparisons are made, as they have been to examine healthcare utilisation and analyse the costs involved in this part of the study. The probability of drawing at least one incorrect conclusion (type-1 error) from a series of hypothesis tests is known as the 'familywise error rate' (FWER). The likelihood of an FWER increases, as the number of comparisons is made (Olejnik et al. 1997; Glenn 2021).

Holm's Sequential Bonferroni Procedure (Holm-Bonferroni correction) is a method of managing type-1 errors when a series of hypothesis tests are undertaken (Holm 1979). Holm's method has greater power than the usual Bonferroni correction and compares the p-value for each of the comparisons conducted, in rank order i.e., the lowest p-value is compared first, the highest p-

value compared last, to the value of the desired p-value (e.g., 0.5, referred to as α) divided by the number of comparisons being tested (m). If first p-value being compared is less than α/m, the null hypothesis is rejected, and the next comparison is made (κ + 1, where κ is the ranking of the p-value in the sorted list). The comparisons are made until the result exceeds α. When that happens, all remaining hypotheses are accepted.

Holm-Bonferroni correction equation

$$\alpha_{Holm\text{-}Bonferroni} = \alpha / m - \kappa + 1$$

Holm-Bonferroni corrections were applied to all statistical output in this phase of the study to ensure hypothesis testing was accurately reported.

7.7.6 Sensitivity analysis

Sensitivity analysis is used to reduce uncertainty in health economic evaluations (Taylor and Filby 2014). Changing one or more parameters allows consideration of which of them most influences the outcome being examined e.g., total cost of healthcare utilisation. One-way and two-way sensitivity analysis was undertaken on healthcare cost data.

Control subject costs were increased by between 25 and 100% for one-way analyses. A two-way analysis was also undertaken where both case and control subject costs were adjusted. In addition to examining cost changes, t-tests were repeated (with a 5% significance level) and Holm-Bonferroni corrections on the adjusted data.

7.7.7 Threshold analysis

Threshold analysis was used to determine how much case subject costs would need to decrease in order to come into line with the control group. Case and control subject costs were recalculated by different percentages. Independent t-tests with a significance level of 5%, were re-run with Holm-Bonferroni correction.

7.8 Results

The Phase 2 study examined the records of 3,286,215 individuals aged 18 years and over. The case group included 657,243 individuals, who had a recorded diagnosis of a non-cancer pain condition and received prescriptions for opioids for a period of time between 2005 and 2015 (Table 7.2). The control group contained 2,628,972 subjects, matched by condition, age, gender and deprivation, who did not have a record of prescriptions for opioids being issued during the study period. The results of statistical analyses between case and control groups are presented in the tables throughout the rest of this chapter. Where comparisons were made within with case or control subject groups (e.g., comparing differences between control subjects by socioeconomic deprivation), they will be presented in the text.

Table 7.2: Demographic data for healthcare utilisation between cases and controls.

Number of subjects	**Case**	**Control**
	657,243	2,628,972
Gender (% of total)		
Male	273,057 (41.5)	1,092,228 (41.5)
Female	384,186 (58.5)	1,536,744 (58.5)
Age		
Mean (SEM)	57.0 (0.02)	57.1 (0.01)
Median	57.0	57.0
Standard deviation	18.1	18.7
Deprivation quintile* (% of total)		
WIMD1	153,649 (23.4)	614,596 (23.4)
WIMD2	136,752 (20.8)	547,008 (20.8)
WIMD3	137,653 (20.9)	550,612 (20.9)
WIMD4	113,083 (17.2)	452,332 (17.2)
WIMD5	116,106 (17.7)	464,424 (17.7)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1=most deprived, WIMD5= least deprived Cases=people receiving opioid prescriptions, Control=not receiving opioid prescriptions

The proportions of men and women were the same in each group (Table 7.2**Error! Reference source not found.**) confirmed using a Chi-square test, χ^2 (df=1, N= 3286215) =.00, p>.999. Mean average ages for cases and controls appeared the same, although a statistically significant difference was found when analysed using an independent t-test, t (df=1039533) =-2.163, p<0.05, d_{Cohen}=0.003. The small statistical difference in age seen between the two groups, was likely due to an age range being used for matching.

7.8.1 Primary Care attendance

Between 2005 and 2015, 190,984,317 general practice appointments were recorded for the 3.2 million people included in the study, with a mean average of 58.1 (SD=97.4) appointments per person. Opioid users accounted for 55% (n=105,457,258) of appointments. Case subjects had significantly more GP visits than control subjects (Table 7.3).

Presentations to General Practice, due to symptoms which could be associated with opioid use (e.g., nausea, vomiting, sedation), were relatively low in number (Table 7.3) but statistically significantly higher for cases than for controls.

Table 7.3: Comparison of Primary Care General Practice utilisation depending on receipt of opioid prescriptions (case versus control)

Total, mean ± (standard deviation)	**Case**	**Control**	**p-value **(d_{Cohen})**
Number of GP attendances	**105,457,258**	**85,527,059**	
Mean (SD)	160.5 (146.3)	32.53 (56.8)	<.001 (0.96)
Median	121.0	10.0	
Prescribing persistence (cases only)			
< 6 months	67.7 (77.6)		
> 6 months	198.8 (150.8)		<.001 (1.3)
Gender			
Female	175.2 (149.1)	36.6 (59.2)	<.001 (1.02)
Male	139.7 (139.6)	26.8 (52.7)	<.001 (0.89)
Deprivation quintile*			
WIMD1	167.2 (149.7)	36.2 (57.7)	<.001 (0.96)
WIMD2	164.7 (148.6)	33.7 (58.9)	<.001 (0.97)
WIMD3	162.3 (147.5)	31.9 (55.8)	<.001 (0.97)
WIMD4	154.9 (144.5)	30.3 (55.5)	<.001 (0.95)
WIMD5	149.8 (137.8)	29.2 (55.3)	<.001 (0.96)
Age group (years)			
18 – 24	41.4 (45.7)	14.9 (21.2)	<.001 (0.62)
25 – 44	93.2 (99.8)	17.9 (31.2)	<.001 (0.83)
45 – 64	144.3 (133.9)	25.9 (44.2)	<.001 (0.98)
65 – 74	207.3 (149.0)	42.3 (64.7)	<.001 (1.22)
75 – 84	250.1 (162.1)	52.6 (79.4)	<.001 (1.32)
≥ 85	250.2 (163.5)	65.0 (86.9)	<.001 (1.21)
GP visits for ADEs possibly associated with opioids	**444,050**	**450,510**	
Mean ± SD	0.68 (2.0)	0.17 (0.7)	<.001 (0.27)
Gender			
Female	0.82 (2.2)	0.21 (0.8)	<.001 (0.30)
Male	0.47 (1.7)	0.11 (0.6)	<.001 (0.23)
Deprivation quintile*			
WIMD1	0.87 (2.5)	0.22 (0.8)	<.001 (0.28)
WIMD2	0.68 (2.0)	0.18 (0.7)	<.001 (0.28)
WIMD3	0.60 (1.7)	0.16 (0.7)	<.001 (0.28)
WIMD4	0.60 (2.0)	0.15 (0.7)	<.001 (0.24)
WIMD5	0.57 (1.6)	0.14 (0.7)	<.001 (0.30)
All tests and referrals from primary care	**206,747**	**158,290**	
Mean ± SD	0.31 (0.9)	0.06 (0.3)	<.001 (0.33)
Recorded imaging (X-ray, CT, MRI etc.)	**90,700**	**74,756**	
Mean ± SD			

	0.14 (0.5)	0.03 (0.2)	<.001 (0.24)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant
Holm-Bonferroni confirmed it was correct to reject the null hypothesis

Significantly more primary care appointments were used by case subjects with prescribing persistence of more than 6 months than those with under 6 months persistence (Table 7.3).

Female case subjects had 25% more primary care appointments than men (t-test, p<.001, d_{Cohen} = 0.25). Thirty-five percent more visits were recorded for women than men in the control group (t-test, p<.001, d_{Cohen} = 0.20).

However, female case subjects had nearly 5 times as many appointments as their controls. The difference between the means of the two groups was statistically significant (Table 7.3). A similar difference was noted between men in the case and control groups in terms of number of primary care appointments (Table 7.3).

Amongst case subjects, the number of primary care attendances was 12% higher for those living in the most deprived areas of Wales (WIMD1) compared to the least deprived (WIMD5) (Table 7.3). There was a greater difference (24%) in the mean number of attendances between the most deprived and the least deprived in the control group, who did not receive prescriptions for opioids. Statistically significant differences were found between all quintiles of both the case subjects (ANOVA, p<.001, h^2_p=.002) and controls (ANOVA, p<.001, h^2_p=.002) which were confirmed between all quintiles by post-hoc analysis.

However, in the most deprived areas (WIMD1), 360% more primary care attendances were recorded in the case group than in the control group (Table 7.3). In the least deprived areas (WIMD5), case subjects visited their GP practice 412% more often than controls.

Primary Care attendance increased with age for cases and controls. In each age-group, however, attendances were significantly higher for people receiving opioid prescriptions (Table 7.3).

ANOVA confirmed statistically significant differences in primary care attendance between age-groups in the case subject group ($p<0.001$, $h^2_p=.160$), although this was not confirmed for the two oldest groups (75-84 years and 85+ years, $p>0.05$) when compared in pairs. Average primary care attendance numbers were significantly different between case subjects in the youngest age-group (age 18 - 24 years) and the oldest (age 85 years and over) ($p<.001$). The oldest age group had 6 times more attendances in Primary Care than the youngest.

The oldest control age group had 4 times more attendances than the youngest (Table 7.3). ANOVA demonstrated significant differences between the mean attendances of all control subject age-groups ($p<0.001$, $h^2_p=.072$) and were confirmed between all age-groups when compared pairwise.

Due to coding restrictions, relatively few tests, referrals and requests for imaging were collected from Primary Care General Practice records. However, based on those made available for analysis, case subjects received 5 times as many tests and imaging appointments than controls (Table 7.3).

7.8.2 Out-Patient attendance

In total 22,239,332 out-patient appointments were recorded for individuals whose data was analysed for this study. Case subjects accounted for 41% (n=9,140,922) of those appointments in absolute terms, despite there being 4 times more people in the control group. However, the average number of out-patient appointments was 2.8 times greater for people receiving opioid prescriptions compared to those who did not (Table 7.4).

Three times more out-patient attendances were noted in case subjects with a prescribing persistence of more than 6 months. It was significantly more than noted in cases with less than 6 months of opioid prescribing persistence.

Differences were maintained between cases and controls when compared by gender (Table 7.4). Female case subjects had on average 25% more out-patient appointments than men (t-test, $p<.001$, $d_{Cohen}=0.25$). In the control group,

women had 30% more out-patient appointments than men (t-test, p<.001, d_{Cohen}=0.22).

Table 7.4: Comparison of out-patient resource utilisation depending on receipt of opioid prescriptions (case versus control)

Total, mean ± standard deviation	Case	Control	p-value** (d_{Cohen})
Number of Outpatient attendances	**9,140,922**	**13,098,410**	
Mean ± SD	13.9 (19.4)	5.0 (10.0)	<.001 (0.50)
Prescribing persistence (cases only)			
< 6 months	5.6 (10.1)		
> 6 months	17.4 (21.2)		<.001 (0.88)
Gender			
Female	15.2 (19.9)	5.5 (10.2)	<.001 (0.52)
Male	12.2 (18.5)	4.2 (9.7)	<.001 (0.46)
Deprivation quintile* * **			
WIMD1	15.2 (20.7)	5.3 (10.0)	<.001 (0.52)
WIMD2	14.4 (19.9)	5.1 (10.4)	<.001 (0.50)
WIMD3	13.5 (19.0)	5.0 (9.7)	<.001 (0.49)
WIMD4	13.0 (18.4)	4.6 (9.3)	<.001 (0.50)
WIMD5	13.0 (18.4)	4.8 (10.7)	<0001 (0.48)
Age group (years)* **			
18 – 24	4.6 (8.1)	1.7 (5.7)	<.001 (0.37)
25 – 44	9.9 (15.0)	3.4 (7.3)	<.001 (0.48)
45 – 64	12.7 (18.7)	4.3 (9.0)	<.001 (0.49)
65 – 74	17.2 (21.9)	7.3 (12.9)	<.001 (0.49)
75 – 84	20.7 (23.3)	7.9 (12.9)	<.001 (0.59)
≥ 85	17.4 (20.5)	5.7 (9.8)	<.001 (0.61)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant ***Holm-Bonferroni confirmed it was correct to reject the null hypothesis

Cases from the most deprived areas of Wales (WIMD1) had 17% more out-patient appointments than those in the least deprived (WIMD5) over the study period. Differences between attendance by case subjects were statistically different when compared by quintile (ANOVA, p<.001, h^2_p=.002). Post-hoc analysis confirmed those differences in all but WIMD4 and WIMD5 quintiles (p>0.5) when attendance was directly compared.

In the control group, that difference was 10%. Comparison of out-patient attendance by deprivation quintile was found to be significant (ANOVA, p<.001, h^2_p=.001), which was confirmed by pairwise comparisons.

When quintiles were directly compared, differences in out-patient attendance between cases and controls was maintained at around 2.7 to 2.8 times more, regardless of deprivation quintile (Table 7.4).

Average number of out-patient appointments per person were greatest in people aged 75 to 84 years, in both case and control groups (Table 7.4). Cases in the 75 to 84 years age-group had 4.5 times more out-patient attendances on average than seen in people aged 18 - 24 years (Table 7.4). Comparisons of out-patient attendances between case subjects of all age-groups were statistically significant (ANOVA, p<.001, h^2_p=.04) and confirmed by pairwise comparisons.

Differences in out-patient attendances groups in control subjects were similar to those seen in cases (Table 7.4). Statistically significant differences in average out-patient attendances were noted between all 6 age-groups (ANOVA, p<.001, h^2_p = .30), confirmed by pairwise comparison.

Observed differences in out-patient attendance between case and control subjects in the same age-groups were around the average noted between cases and controls overall. Three times more out-patient appointments were noted in cases than controls in the ≥85 years age group (Table 7.4).

7.8.3 Emergency Department Utilisation

Between 2005 and 2015, 2,810,268 Emergency Department (ED) attendances were recorded for the 3,286,215 individuals included in the study, averaging 0.9 ± 2.2 appointments per person.

On average, more than 3 times as many emergency department (ED) attendances per person (Table 7.5**Error! Reference source not found.**), and for any reason, were observed in the case subject group than the control group during the study period.

Table 7.5: Comparison of Emergency department resource utilisation depending on receipt of opioid prescriptions (case versus control)

Total, mean (standard deviation)	**Case**	**Control**	**p-value** (d_{Cohen})**
Number of Emergency Department attendances	**1,243,641**	**1,566,627**	
	1.89 (3.4)	0.6 (1.8)	<.001 (0.42)
Prescribing persistence (cases only)			
< 6 months	0.96 (1.9)		
> 6 months	2.3 (3.8)		<.001 (0.00.51)
Gender			
Female	1.9 (3.4)	0.58 (1.7)	<.001 (0.42)

	Male	1.9 (3.4)	0.61 (1.8)	<.001 (0.40)
Deprivation quintile*				
	WIMD1	2.3 (3.9)	0.77 ± 2.1	<.001 (0.42)
	WIMD2	2.4 (3.8)	0.65 ± 1.7	<.001 (0.40)
	WIMD3	1.8 (3.2)	0.55 ± 1.9	<.001 (0.42)
	WIMD4	1.64 ± 2.9	0.53 ± 1.4	<.001 (0.42)
	WIMD5	1.5 ± 2.6	0.41 ± 1.2	<.001 (0.46)
Age group (years)				
	18 – 24	2.0 ± 3.9	0.86 ± 2.2	<.001 (0.32)
	25 – 44	2.2 ± 3.8	0.61 ± 1.5	<.001 (0.47)
	45 – 64	1.7 ± 3.2	0.56 ± 1.7	<.001 (0.37)
	65 – 74	1.5 ± 3.1	0.56 ± 2.2	<.001 (0.33)
	75 – 84	2.0 ± 3.1	0.58 ± 1.6	<.001 (0.48)
	≥ 85	2.5 (3.3)	0.67 (1.6)	<.001 (0.61)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant
Holm-Bonferroni confirmed it was correct to reject the null hypothesis

Case subjects receiving opioid prescriptions for more than 6 months attended emergency departments 2.4 times more often than those with shorter durations of prescribing (Table 7.5).

Female and male case subjects had over 3 times more ED attendances compared to their respective controls (Table 7.5**Error! Reference source not found.**). However, no statistical difference was found between male and female case subjects (p=0.534, d_{Cohen} = 0.002), in terms of average number of attendances. However, female controls had significantly more ED attendances than male controls (p<.001, d_{Cohen} = 0.004).

Case subjects average attendance at ED had little numerical difference in the 2 most deprived quintiles (WIMD1 and WIMD2) although pairwise comparisons derived a statistically significant difference between them (p<.001) (Table 7.5**Error! Reference source not found.**). Around 50% more ED attendances were recorded in the two most deprived quintiles than the least deprived (WIMD5) for case subjects. Mean attendances increased as deprivation increased and the differences between quintiles were statistically significant (ANOVA, p<.001, h^2_p=.007).

There was slightly more difference (18%) in the control group, in terms of average number of attendances between the lowest two quintiles (WIMD1 and WIMD2) (Table 7.5). However, 88% more ED attendances happened in the most

deprived quintile of controls, compared to the least (WIMD5). As with cases, there was a significant difference between control subjects' average attendances between quintiles. Greater levels of deprivation were associated with higher numbers of ED attendance (ANOVA, $p<.001$, $h^2 = 0.005$). Differences in attendance numbers were significant between all quintiles when control subjects were compared in pairs.

Overall, 3 times more ED appointments were recorded for case subjects in the most deprived quintile compared to controls (Table 7.5**Error! Reference source not found.**). This rose to 3.7 times more appointments by cases compared to controls in the least deprived quintile.Two-way ANOVA demonstrated however, that deprivation was not a lone influence for attendance (Appendix F).

The average number of emergency department attendances were lowest in the age group 65 to 74 years for both case and control subjects (Table 7.5**Error! Reference source not found.**).

In the case subject group, the highest average number of attendances was noted in the oldest age-group (≥ 85 years). This was 66% higher than in the lowest age group. Comparisons of mean attendances determined significant differences between each age-group when analysed as a group and in pairs (ANOVA, $p<.001$, $h^2_p=.009$).

In the control group, the highest number of average ED attendances were observed in 18- to 24-year-olds, 53% more than seen in the 65 to 74 years age-group. Statistically significant differences in mean attendances were noted between all age-groups of control subjects (ANOVA, $p<.001$, $h^2_p=.001$). Pairwise comparison confirmed differences between age groups other than the 45 – 64 years and ≥ 85 years groups where a statistical difference was not found ($p>0.1$).

7.8.4 In-Patient attendance and Length of Stay

Case subjects had on average twice as many hospital admissions as controls, which was statistically significant (

Table 7.6). Length of Stay (LoS) was however, on average, 6% longer for control subjects and was statistically significant, albeit with a smaller effect size than noted for number of admissions.

Table 7.6: Comparison of In-patient admission and length of stay depending on receipt of opioid prescriptions (case versus control)

Total, mean (standard deviation)	Case	Control	p-value** (d_{Cohen})
Number of In-patient admissions	**3,021,645**	**5,676,577**	
Mean ± SD	4.6 (8.5)	2.2 (6.3)	<.001 (0.30)
Prescribing persistence (cases only)			
< 6 months	2.9 (6.2)		
> 6 months	5.3 (9.2)		<.001 (0.47)
Gender			
Female	5.0 (8.1)	2.3 (6.0)	<.001 (0.34)
Male	4.1 (9.0)	2.0 (6.7)	<.001 (0.25)
Deprivation quintile			
WIMD1	4.9 (8.1)	2.3 (4.8)	<.001 (0.35)
WIMD2	4.8 (8.7)	2.2 (4.7)	<.001 (0.32)
WIMD3	4.5 (8.3)	2.3 (8.3)	<.001 (0.26)
WIMD4	4.4 (9.0)	2.0 (6.4)	<.001 (0.29)
WIMD5	4.2 (8.3)	1.9 (6.9)	<.001 (0.29)
Age group (years)			
18 – 24	3.5 (6.5)	0.5 (2.1)	<.001 (0.49)
25 – 44	3.9 (7.4)	1.0 (2.7)	<.001 (0.44)
45 – 64	3.5 (7.8)	1.2 (4.8)	<.001 (0.30)
65 – 74	5.0 (9.3)	3.1 (10.0)	<.001 (0.20)
75 – 84	6.9 (10.1)	4.6 (6.0)	<.001 (0.25)
≥ 85	8.3 (8.6)	5.1 (9.3)	<.001 (0.37)
Length of stay (days)	**10 758 522**	**45 482 557**	
Mean ± SD	16.4 (54.7)	17.3 (64.9)	<.001 (-0.02)
Prescribing persistence (cases only)			
< 6 months	10.4 (46.7)		
> 6 months	18.8 (57.5)		<.001 (0.37)
Gender			
Female	18.0 (57.0)	19.3 (68.2)	<.001 (-0.02)
Male	14.1 (51.3)	14.5 (60.0)	<.001 (-0.01)
Deprivation quintile			
WIMD1	17.6 (58.6)	17.9 (65.8)	<.001 (-0.006)
WIMD2	16.9 (56.4)	18.0 (72.9)	<.001 (-0.02)
WIMD3	16.5 (53.6)	18.9 (62.1)	<.001 (-0.04)
WIMD4	15.0 (49.6)	15.1 (55.8)	0.710 (-.001)
WIMD5	15.3 (53.4)	15.9 (65.4)	<.001 (-0.01)
Age group (years)			
18 – 24	5.1 (22.4)	0.8 (7.0)	<.001 (0.20)
25 – 44	6.8 (33.4)	1.8 (21.1)	<.001 (0.16)
45 – 64	8.1 (40.0)	5.0 (37.7)	<.001 (0.08)
65 – 74	15.5 (50.9)	20.5 (66.9)	<.001 (-0.09)
75 – 84	34.6 (78.8)	50.3 (108.2)	<.001 (-0.18)
≥ 85	67.7 (96.0)	70.3 (110.1)	<.001 (-0.03)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant Holm-Bonferroni confirmed it was correct to reject the null hypothesis

Case subjects who received opioid prescriptions persistently for more than 6 months had significantly more hospital admissions than those with less persistent prescribing. Both average number of admissions and average LoS were 80% higher in those with longer prescription persistence (

Table 7.6).

Female case subjects had 22% more hospital admissions per person than were noted for male cases. The difference in mean number of admissions was statistically significant (t-test, $p<.001$, $d_{Cohen}=0.10$). LoS was significantly longer for female than male cases, with an average of 4 days greater duration (t-test, $p<.001$, $d_{Cohen}=0.07$) (

Table 7.6).

Amongst controls, females had an average 15% more hospital admissions, which, was significantly more than for male controls but with a small effect size (t-test, $p<.001$, $d_{Cohen}=0.05$). Female controls also had significantly greater lengths of stay) than men (t-test, $p<.001$, $d_{Cohen}=0.08$).

Comparing cases and controls, female and male case subjects had on average, twice as many admissions per person as for their comparators in the control groups (

Table 7.6). These statistically significant differences in admissions were reversed when analysing LoS. Female controls stayed on average 1.3 days longer than female case subjects. Male controls had a smaller difference in LoS compared to their matched case subjects. It was still considered statistically significant, however (

Table 7.6).

Greater socio-economic deprivation was associated with a higher number of in-patient admissions and a longer duration of stay (

Table 7.6). Case subjects in the most deprived areas of Wales (WIMD1) had an average 16% more admissions than those in the least (WIMD5) deprived. Mean average number of case subject admissions were significantly higher with increasing deprivation (ANOVA, $p<.001$, $h^2_p=.001$) and confirmed by pairwise comparison. Case subject length of in-patient stay was also longer for those in more deprived areas (

Table 7.6) Duration of admission had an average 15% difference between most and least deprived areas. Comparisons determined statistically significant differences between LoS in each quintile and confirmed by pairwise comparisons (ANOVA, $p<.001$, $h^2_p=.0003$).

Higher numbers of admissions and LoS were also noted with increasing deprivation for the control group (

Table 7.6). A 21% difference in number of in-patient admissions was noted between WIMD1 and WIMD5 quintiles and deemed statistically significant (ANOVA, $p<.001$, $h^2_p=.001$). The longest LoS in the control group was seen in the middle quintile (WIMD3) (

Table 7.6). There was a difference of 3 days between shortest and longest average LoS in the control group. Average LoS was determined to be significantly different between all quintiles and confirmed by pairwise comparisons (ANOVA, $p<.001$, $h^2_p=.002$).

When quintiles were compared by case versus control, average numbers of admissions were greater in all case subjects (

Table 7.6). The third quintile (WIMD3) revealed a 15% longer average admission for controls compared to case subjects. However, all comparisons demonstrated significantly longer duration of admission in the control group compared to the case subjects, regardless of quintile.

Both case and control subjects demonstrated an overall increase in number of in-patient admissions and LoS with advancing age (

Table 7.6). Amongst case subjects, there were 2.4 times as many admissions on average in the 85+ years group compared to the 18 – 24 years group. There were the same average number of admissions however, for 18-24 years and 45-64 years age groups. Statistically significant differences were confirmed between all case subject age-groups (ANOVA, $p<.001$, $h^2_p=.031$) other than 18-24 years and 45-64 years groups where pairwise comparison demonstrated no statistical difference in the number of admissions.

Thirteen times longer average lengths of in-patient admission were observed in the oldest case subjects compared to the youngest. Three days was the difference in average admission length (

Table 7.6) between the three-younger age-groups (from 18–64 years). Admission duration then doubled with each advancing age-group. The changes in LoS between age-groups were considered significant when compared between case subject age-groups (ANOVA, $p<.001$, $h^2_p=.092$).

For control subjects, ten times more admissions were noted on average, for individuals aged 85 and above compared to the youngest group. As with case subjects, the control group showed a similar pattern of similar average number of admissions in the younger age groups with a widening gap as age increased. Differences between age-group ranked admissions were statistically significant and confirmed by direct pairwise comparisons (ANOVA, $p<.001$, $h^2_p=.058$).

Control group lengths of stay spanned 69.5 days on average, between the youngest and oldest. Eighty-eight times more days on average were spent in hospital by control subjects aged 85 years and over, compared to those aged 18-24 years (

Table 7.6). Differences in average LoS by age-group were statistically significant (ANOVA, $p<.001$, $h^2_p=.116$) and confirmed by pairwise comparison.

Analysing case and control subjects within the same age groups revealed interesting differences. Between 18 and 64 years, case subjects had significantly more admissions and a longer in-patient stay than their equivalent controls (

Table 7.6). Case subjects aged 18-24 years had 7 times more admissions and 6.4 times longer average admission duration compared to their controls for example (

Table 7.6).

After 65 years old however, the pattern changed. Case subjects had a significantly higher average number of admissions per person, although the duration of stay was longer in the control group. For example, the age group 75-84 control subjects had 50% more admissions on average than their controls but with 30% shorter average LoS (

Table 7.6).

7.9 Regression Analysis

Multiple linear regression analyses were used to predict which, if any, variables affected attendance in Primary Care (number of GP visits), out-patient, emergency department or in-patient attendances. The factors used to make the predictions were opioid prescription, age, gender, deprivation status (WIMD2011), recorded diagnosis of depression and/or anxiety and whether opioids were prescribed, and if they were prescribed for more or less than 6 months.

7.9.1 Primary Care General Practice attendance

Multiple linear regressions results indicated that the model was a significant predictor of the number of attendances in Primary Care (GP), F (10, 3286204) = 276498.2, p<.001. An R^2 of 0.457, SE=71.8 (R = 0.676) meant 45.7% of the variation in the original data could be explained by this model. The $ß_0$ (constant) for the regression equation was -26.24, SE=.138, p<.001.

Based on the regression output (Table 7.7), the strongest predictors for attendance in Primary Care (GP) were prescription duration of more than 6 months ($ß_n$=143.50, SE=.121, p<.001), which increased GP attendance by 143.5 visits compared to an increase of 34.3 visits for less than 6 months ($ß_n$=34.33, SE=.171, p<.001). Having a recorded diagnosis of depression ($ß_n$=22.979, SE=.123, p<.001) increased primary care attendance by 23 visits. However, living in the least deprived areas of Wales (WIMD5) decreased GP attendance by 7.2 visits ($ß_n$=-7.18, SE=.126, p<.001), compared to living in the most deprived areas (WIMD1). Being male reduced likelihood of GP attendance by 10.4 visits ($ß_n$=-10.42, SE=.081, p<.001).

Table 7.7: Output from multiple linear regression to predict Healthcare utilisation by visits or attendances

Variable $ß_n$ (SE)	GP visits		Outpatient visits	ED visits	Inpatient admission
Age	17.698 (.031)	17.208 (.033)	1.399 (.005)	.007 (.001)	.786 (.002)
Deprivation quintile*					
WIMD2	-2.122 (.119)	-3.789 (.125)	-.342 (.020)	-.128 (.004)	-.173 (.009)
WIMD3	-3.780 (.119)	-6.983 (.125)	-.717 (.020)	-.241 (.004)	-.156 (.009)
WIMD4	-5.845 (.126)	-9.456(.132)	-1.087 (.021)	-.275 (.004)	-.394 (.010)
WIMD5	-7.180 (.126)	-12.017(.132)	-.974 (.021)	-.382 (.004)	-.530 (.010)
Gender (male)	-10.419 (.081)	-11.298 (.084)	-1.240 (.014)	.068 (.002)	-.227 (.006)
Duration of prescribing					
Under six months	34.329 (.171)	40.671 (.178)	.777 (.029)	.300 (.005)	-.392 (.013)
Over six months	143.501 (.121)	163.975 (.119)	11.649 (.020)	1.540 (.004)	1.614 (.009)
Depression	22.979 (.123)		2.430 (.021)	.633 (.004)	.737 (.009)
ED Visits	9.282 (.018)				
p-value**	<.001	<.001	<.001	<.001	<.001

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant

The regression was repeated, removing attendance at the emergency department and diagnosis of depression and/or anxiety as a predictive variable (Table 7.7). Emergency department attendance numbers appeared quite low for the number of subjects in the study. Therefore, from a clinical perspective, it was assumed removing ED attendance from the model would not lead to substantial change. Depression and/or anxiety might be a reason to visit the GP in itself, so it was interesting to review the impact of removing it from the model. The resulting regression equation remained significant, F (8, 3286206) = 280702.3, p<.001, R^2 = 0.406, SE=75.0 (R = 0.627). In this case, 40.6% of the variance in the data was explained by the model. The $ß_0$ (constant) for the regression equation was -14.1, SE=.142. Consequently, removing ED attendance and depression/anxiety from consideration weakened the model slightly.

In the second model, receiving opioid prescriptions and for longer than 6 months ($ß_n$=163.97, SE=.119, p<.001) remained the most influential factors for having an appointment at in Primary Care, adding 164 visits (Table 7.7). Receiving opioid prescriptions for less than six months ($ß_n$=40.67, SE=.178, p<.001) added 40 visits compared to controls. Deprivation quintile had an inverse effect on GP attendance i.e., lower quintile increased attendance. Age was positively associated with primary care visits ($ß_n$=17.21, SE=.033, p<.001), with an increase of 17 visits per year, from age 18 years onwards.

7.9.2 Out-patient attendance

The multiple linear regression equation for predicting out-patient attendance was deemed significant F (9, 3286205) = 56629.0, p<.001, R^2 = 0.134, SE=12.1 (R = 0.366) (Table 7.7). However, this model only accounted for 13.4% of the variables that might predict the number of out-patient attendances of an individual. The $ß_0$ (constant) for the out-patient regression equation was 1.2, SE=.023.

In this equation, being prescribed opioids for more than 6 months ($ß_n$=11.65, SE=.020, p<.001) was demonstrated to be significant in increasing the likelihood

of out-patient appointments. In this model, being resident in the most deprived areas (WIMD1) was taken as baseline, whilst all other quintiles reduced the likelihood of having an outpatient appointment (Table 7.7). A diagnosis of depression and/or anxiety had a greater positive effect ($ß_n$=2.4, SE=.021, p<.001) on outpatient visits than receiving opioid prescription for less than six months ($ß_n$=.78, SE=.029, p<.001) although both were considered statistically significant.

7.9.3 Emergency Department attendance

Multiple linear regression to predict the number of Emergency Department attendances gave a statistically significant result (Table 7.7) but was only reliable for 8.1% of the variance within the model, F (9, 3286205) = 32121.3, p<.001, R^2 = 0.081, SE=2.14 (R = 0.284). In this equation, the constant $ß_0$ was 0.68, SE=.004.

In the model, recorded diagnosis of depression and/or anxiety ($ß_n$=.633, SE=.004, p<.001) and receiving opioid prescriptions for more than 6 months ($ß_n$=1.540, SE=.004, p<.001) appeared to have more impact on ED attendance although none of the predictive variables were notable.

7.9.4 Number of In-patient admissions

The multiple linear regression equation for predicting the number of in-patient admissions was not effective (Table 7.7). Whilst a statistically significant result was obtained, the model was only able to predict around 7% of the variance within it, F (9,3286205) = 18090.5, p<.001, R^2 = 0.047 (R = 0.217), $ß_0$ = -.628, SE=.011.

As with predicting out-patient attendances, a diagnosis of depression and/or anxiety ($ß_n$=.737, SE=.009, p<.001) and being prescribed opioids for more than 6 months were the variables which appeared to exert most influence on the number of in-patient admissions. Increasing levels of deprivation had an inverse influence on the likelihood of in-patient admission. Male gender was significant factor albeit negative influence for predicting hospital admission.

7.10 Cost Analysis

7.10.1 Total Healthcare costs

Taking the costings from the 3.2 million subjects included in this study, the average cost of Healthcare utilisation (Primary and Secondary Care) was estimated to be £11,096.49 ± 15.03 per person (Table 7.8**Error! Reference source not found.**) over the 11-year study period. Costs for the case group receiving opioid prescriptions (£16,453.35 ± 33.08 per person) were estimated to be £6696.08 per person (CI 95% £6,623.39 – £6,768.77, p<.001, $d_{Cohen's}$=.25) more than for people in the control group (£9,757.27 ± 16.77). There was a 68%. difference in costs between the two groups (Table 7.8)

Using actual subject numbers (Section 7.4.2) estimated that the total healthcare cost for all subjects whether case or control, with recorded diagnoses of osteoarthritis, rheumatoid arthritis, neck pain, back pain, fibromyalgia, or neuropathic pain was £11.8 billion, between 2005 and 2015. That averaged just under £1.1 billion per year. Healthcare costs for people with those conditions and receiving opioid analgesics (case subjects) averaged £0.9 billion per year between 2005-2015, without factoring in medication costs. The data used for this study was representative of 78% of the Welsh population, so assuming this was a representative population, annual healthcare costs could be as much as £1.3 billion for those with the listed diagnoses with £1.2 billion allocated to those also receiving opioid medicines.

7.10.2 Costs for specified services

The average cost of total Primary Care attendance including tests and investigations, by individuals included in this study was estimated to be £2,003.23 ± £1.85 (SEM) per person (Table 7.8**Error! Reference source not found.**). The average cost of Primary Care attendance in the opioid group was 4.9 times per person higher than in the control group. The differences in all Primary Care costs between the two groups were statistically significant (Table 7.8**Error! Reference source not found.**).

Table 7.8: Average costings per person for healthcare utilisation comparing all subjects within the study, cases and controls.

Variable	Mean average costs per person (£) (standard error of the mean)				
	All subjects (n = 3 286 215)	**Cases (n = 657 243)**	**Controls (n = 2 628 972)**	**Difference (95% CI)**	**p-value** ($d_{Cohen's}$)**
Primary care					
GP appointments	2002.71 (1.85)	5529.24 (6.22)	1121.07 (1.21)	4408.17 (4395.76 – 4420.59)	<.001 (0.96)
Potential opioid ADEs*	9.38 (0.02)	23.28 (0.09)	5.91 (0.02)	17.37 (17.21 – 17.55)	<.001 (0.27)
Tests and investigations	0.52 (.001)	1.52 (0.01)	0.27 (.001)	1.25 (1.24 – 1.26)	<.001 (0.33)
Imaging	4.39 (0.01)	12.03 (0.05)	2.48 (0.01)	9.55 (9.45 – 9.66)	<.001 (0.24)
Total Primary Care	2003.23 (1.85)	5530.77 (6.22)	1121.34 (1.21)	4409.43 (4397.01 – 4421.84)	<.001 (0.96)
Emergency department					
Any ED attendance	112.81 (0.16)	249.62 (0.55)	78.61 (0.14)	171.01 (169.89 – 172.12)	<.001 (0.42)
ED attendance for pain	0.63 (0.01)	0.89 (0.02)	0.57 (0.01)	0.32 (0.29 – 0.35)	<.001 (0.03)
ED attendance for opioid ADEs*	0.56 (0.01)	1.00 (0.02)	0.45 (0.01)	0.55 (0.52 – 0.59)	<.001 (0.04)
Secondary Care					
Outpatient attendance	744.69 (0.79)	1530.43 (2.34)	548.26 (0.68)	982.18 (976.84 – 987.52)	<.001 (0.50)
Day case acute care attendance	779.64 (2.01)	1605.80 (5.46)	573.10 (2.09)	1032.70 (1021.25 – 1044.51)	<.001 (0.24)
In-patient admission – standard	5676.42 (6.73)	5073.20 (12.43)	5935.49 (7.98)	-862.29 (891.25 – 833.34)	<.001 (0.16)
In-patient admission – excess days	8669.82 (21.76)	4579.52 (26.81)	10426.56 (28.75)	-5847.04 (5924.09 – 5768.99)	<.001 (-0.06)
Total in-patient	7456.11 (13.94)	7536.73 (27.97)	7435.96 (15.96)	100.77 (32.20 – 37.66)	<.001 (0.004)
Total secondary care	8235.76 (14.27)	9142.53 (29.25)	8009.06 (16.27)	1133.47 (1067.88 – 1199.07)	<.001 (0.05)
Total healthcare costs per person	**11096.49** (15.03)	**16453.35** (33.08)	**9757.27** (16.77)	**6696.08** (6623.39 – 6768.77)	**<.001 (0.25)**

*ADE = adverse events, side-effects from medication **p-value calculated from t-test (case-control), <0.05 = significant Holm-Bonferroni tests confirmed it was correct to reject the null hypothesis

Whilst the numbers of attendances for potential opioid adverse events were low for both cases and controls, costs for the opioid group were 3.9 times per person higher than for the control group (Table 7.8). Similarly, whilst only limited data was available on tests and investigations, 5.6 times higher costs per person were incurred by the opioid group compared to the control group. Imaging costs averaged at £4.39 ± £0.01 per person, with case subjects incurring 4.9 times the costs of their controls (Table 7.8).

Costs associated with ED attendance incurred by those receiving opioid prescriptions were twice those of the control group (Table 7.8). Costs for ED attendances for possible opioid adverse events were, on average, lower than those for pain. The cost of pain-related attendances and adverse events that may be associated with opioid use, were significantly higher for case subjects than for the control group (Table 7.8**Error! Reference source not found.**).

Outpatient attendance costs for those in receipt of opioid prescriptions were 2.8 times higher than for people in the control group which was a statistically significant difference (Table 7.8). Average day case attendance costs per person in the study group were £744.69 ± £0.79. Costs for case subjects were 2.8 times higher than for the control group (Table 7.8**Error! Reference source not found.**).

In-patient attendance was divided into standard admission, up to 5 days in a single admission and excess days, costed from day of admission onwards. Standard admission costs averaged £5676.42 ± £6.73 per person and in a reversal of previous results, the costs were significantly higher in the control group than for the case (Table 7.8**Error! Reference source not found.**). In-patient excess days had a total average cost of £8669.82 ± £21.76 per person. Control subjects incurred 2.3 times more excess days costs than cases (Table 7.8Error! Reference source not found.).

7.10.3 Examining costs by demographic factors

7.10.3.1 Gender

Healthcare costs were 66% higher in female case subjects compared to their controls. (Table 7.9). Average male expenditure was 30% less than for female subjects. Male case subjects had on average 73% greater total healthcare costs compared to their controls (Table 7.9).

Table 7.9: Average costings by gender for healthcare utilisation, comparing cases and controls

		Mean average costs (£) (standard error of the mean)				
		All subjects	**Cases**	**Controls**	**Difference (95% CI)**	**p-value*** ($d_{Cohen's}$)
Female		n = 1 920 930	n = 384 186	n = 1 536 744		
	Primary care	2216.46 (2.52)	6037.93 (8.29)	1261.10 (1.65)	4778.30 (4761.74 – 4794.87)	<.001 (1.02)
	Emergency Department	111.68 (0.21)	249.91 (0.72)	77.13 (0.18)	172.78 (171.34 – 174.23)	<.001 (0.42)
	Secondary Care	9093.64 (19.44)	9985.20 (39.46)	8870.75 (22.21)	1114.46 (1-25.70 – 1203.21)	<.001 (0.04)
	Total	**12 243.43** (20.42)	**17942.03** (44.45)	**10818.78** (22.84)	**7123.25** (7025.31 – 7221.18)	**<.001** (0.26)
Male		n = 1 365 285	n = 273 057	n = 1 092 228		
	Primary care	1701.95 (2.66)	4813.54 (9.21)	924.06 (1.74)	3890.42 (3872.05 – 3908.78)	<.001 (0.89)
	Emergency Department	114.41 (0.26)	249.21 (0.86)	80.71 (0.23)	168.51 (166.76 – 170.26)	<.001 (0.40)
	Secondary Care	7028.73 (20.74)	7956.91 (43.17)	6796.68 (23.57)	1160.22 (1063.83 – 1256.62)	<.001 (0.05)
	Total	**9482.76** (21.91)	**14358.81** (49.01)	**8263.74** (24.35)	**6095.07** (5987.81 – 6202.33)	**<.001** (0.24)

*p-value calculated from t-test (case-control), <0.05 = significant Holm-Bonferroni confirmed it was correct to reject the null hypothesis

7.10.3.2 Deprivation

Increased costs were associated with increased levels of socioeconomic deprivation in primary care, emergency department and overall healthcare costs (Table 7.10) within case and control groups. Examining costs by deprivation quintiles revealed significantly higher average costs in case subjects than controls in every measure examined.

Table 7.10: Average costings per person by deprivation for healthcare utilisation comparing cases and controls

	Mean average costs per person (£) ± SEM				
	All subjects (n = 3 286 215)	**Cases** (n = 657 243)	**Controls** (n = 2 628 972)	**Difference (95% CI)**	**p-value*** ($d_{Cohen's}$)
Total Primary care					
WIMD1	2149.60 (3.91)	17509.49 (72.18)	10283.28 (35.11)	4516.81 (4500.53 – 4533.10)	<.001 (0.96)
WIMD2	2064.27 (4.15)	16953.81 (74.62)	10068.36 (40.24)	4513.87 (4486.19 – 4541.55)	<.001 (0.97)
WIMD3	1998.26 (4.07)	16489.79 (71.41)	10475.45 (36.00)	4494.55 (4467.15 – 4521.94)	<.001 (0.97)
WIMD4	1902.76 (4.38)	15530.13 (74.56)	8680.84 (35.40)	4294.40 (4264.84 – 4323.96)	<.001 (0.95)
WIMD5	1838.42 (4.19)	15322.23 (75.78)	8891.71 (39.82)	4155.40 (4127.54 – 4183.26)	<.001 (0.96)
Emergency department					
WIMD1	142.06 (0.40)	303.46 (1.32)	101.71 (0.36)	201.75 (199.06 – 204.44)	<.001 (0.42)
WIMD2	122.78 (0.38)	269.27 (1.35)	86.07 (0.31)	183.52 (180.81 – 186.22)	<.001 (0.40)
WIMD3	105.45 (0.36)	236.78 (1.14)	72.61 (0.34)	164.17 (161.84 – 166.49)	<.001 (0.42)
WIMD4	99.79 (0.33)	216.99 (1.13)	70.49 (0.28)	146.50 (144.22 – 148.79)	<.001 (0.46)
WIMD5	83.80 (0.28)	201.86 (1.02)	54.29 (0.29)	147.57 (145.52 – 149.62)	<.001 (0.46)
Total Secondary Care					
WIMD1	8634.71 (30.06)	9775.70 (64.20)	8349.47 (33.96)	1426.23 (1283.88 – 1568.58)	<.001 (0.6)
WIMD2	8487.79 (34.11)	9421.72 (66.13)	8254.31 (39.29)	1167.40 (1016.65 – 1318.16)	<.001 (0.05)
WIMD3	8839.61 (30.63)	9174.16 (62.92)	8755.97 (34.91)	418.19 (277.11 – 559.22)	<.001 (0.02)
WIMD4	7358.20 (30.32)	8542.16 (65.20)	7062.20 (34.20)	1479.96 (1335.65 – 1624.27)	<.001 (0.07)
WIMD5	7549.73 (33.75)	8523.04 (67.18)	7306.40 (38.69)	1216.64 (1064.69 – 1368.58)	<.001 (0.05)
Total costs					
WIMD1	11728.52 (31.75)	17509.49 (72.18)	10283.28 (35.11)	7226.21 (7068.89 – 7383.53)	<.001 (0.26)
WIMD2	11445.45 (35.64)	16953.81 (74.62)	10068.36 (40.24)	6885.45 (6719.28 – 7051.62)	<.001 (0.25)
WIMD3	11678.32 (32.28)	16489.79 (71.41)	10475.45 (36.00)	6014.34 (5857.60 – 6171.08)	<.001 (0.23)
WIMD4	10050.70 (32.21)	15530.13 (74.56)	8680.84 (35.40)	6849.29 (6687.53 – 7011.05)	<.001 (0.28)
WIMD5	10177.81 (35.44)	15322.23 (75.78)	8891.71 (39.82)	6430.52 (6262.73 – 6598.31)	<.001 (0.25)

*p-value calculated from t-test (case-control), <0.05 = significant.
Holm-Bonferroni confirmed it was correct to reject the null hypothesis

7.10.3.3 Prescribing Persistence

Significantly greater costs were noted for people receiving more than 6 months of opioid prescriptions for all healthcare resources examined (Table 7.11). Average total healthcare costs were estimated to be 122% higher when opioid prescriptions persisted for more than 6 months.

Table 7.11: Average costings per person for healthcare utilisation comparing all opioid prescribing persistence of less or more than 6 months

Healthcare resource	Opioid prescribing persistence			
	< 6 months (n = 192281)	**> 6 months** (n =464962)	**Difference (95% CI)**	**p-value*** ($d_{Cohen's}$)
Primary care	2333.25 (6.09)	6850.92 (7.62)	4518.94 (4499.82 – 4538.07)	<.001 (1.25)
Emergency department	126.47 (0.58)	300.55 (0.73)	174.07 (172.25 – 175.90)	<.001 (0.51)
Secondary Care	5760.49 (44.52)	10541.14 (36.82)	4780.65 (4667.42 – 4893.89)	<.001 (0.22)
Total costs	**8835.89** (46.94)	**19603.49** (41.68)	**10767.60** (10644.57 – 10890.62)	**<.001** (0.47)

*p-value calculated from t-test (case-control), <0.05 = significant
Holm-Bonferroni confirmed it was correct to reject the null hypothesis

7.10.3.4 One-way sensitivity analysis

Increasing control group costs for Primary care attendance, up to double of those observed in the study, did not result in a non-significant difference (acceptance of the null hypothesis). Doubling of control group primary care costs, resulted in a 2.5 times lower costs per person, which remained significantly less than for the unchanged case group. Doubling of emergency department attendance costs also failed to lead to acceptance of the null hypothesis.

Secondary care and consequently total healthcare costs, when increased by 75% and above, became higher in the control group than for case subjects, with the difference being statistically significant.

Overall, the sensitivity analyses demonstrate that increases of more than 50% in healthcare attendances and therefore, costs, would be needed in the control group in order to bring the totals in that group, close to those noted in case subjects.

Table 7.12: Comparison of costs per person for sensitivity analysis: study estimates of case subject costs compared to re-calculated control subject costs

	Mean average costs per person (£) ± standard error of the mean			
Increase to control subjects' costs	**Cases** (n = 657 243)	**Controls** (n = 2 628 972)	**Difference (95% CI)**	**p-value*** ($d_{Cohen's}$)
Total Primary care				
25%	5530.77 (6.21)	1401.68 (1.51)	4129.09 (4116.54 – 4141.63)	<.001 (0.89)
50%	5530.77 (6.21)	1682.02 (1.81)	3848.75 (3836.06 – 3861.45)	<.001 (0.82)
75%	5530.77 (6.21)	1962.35 (2.11)	3568.42 (3555.54 – 3581.29)	<.001 (0.75)
100%	5530.77 (6.21)	2242.69 (2.42)	3288.08 (3275.00 – 3301.16)	<.001 (0.68)
Emergency department				
25%	249.62 (0.55)	98.27 (0.18)	151.36 (150.22 – 152.49)	<.001 (0.36)
50%	249.62 (0.55)	117.92 (0.21)	131.70 (130.54 – 132.86)	<.001 (0.31)
75%	249.62 (0.55)	137.57 (0.25)	112.05 (110.86 – 113.23)	<.001 (0.26)
100%	249.62 (0.55)	157.23 (0.28)	92.40 (91.18 – 93.61)	<.001 (0.0.20)
Total Secondary Care				
25%	9142.53 (29.25)	10011.33 (20.34)	-868.80 (-953.52 - -784.07)	<.001 (-0.03)
50%	9142.53 (29.25)	12013.59 (24.41)	-2871.06 (-2945.72 - -2896.40)	<.001 (-0.10)
75%	9142.53 (29.25)	14015.86 (28.48)	-4873.33 (-4953.33 - -4793.32)	<.001 (-0.17)
100%	9142.53 (29.25)	16018.12 (32.55)	-6875.59 (-6961.35 - -6789.83)	<.001 (-0.22
Total costs				
25%	16453.35 (33.08)	12196.59 (20.96)	4256.76 (4180.01 – 4333.52)	<.001 (0.15)
50%	16453.35 (33.08)	14635.91 (25.15)	1817.45 (1736.00 – 1898.89)	<.001 (0.06)

75%	16453.35 (33.08)	17075.22 (29.34)	-621.87 (-708.54 - -535.21)	<.001 (-0.02)
100%	16453.35 (33.08)	19514.54 (33.53)	-3061.19 (-3153.51 - -2968.87)	<.001 (-0.09)

*p-value calculated from t-test (case-control), <0.05 = significant Holm-Bonferroni confirmed it was correct to reject the null hypothesis

7.10.3.5 Two-way sensitivity analysis

Alterations made to both case and control subject costs, did not result in a non-significant difference between the groups (Table 7.13). When primary care costs were adjusted in order to produce a difference of £18.99. The difference was still considered statistically significant – likely due to the large numbers of subjects, as the effect size was negligible (Table 7.13).

Table 7.13: Comparison of costs per person for sensitivity analysis: study estimates of re-calculated case and control subject costs

	Mean average costs per person (£) (standard error of the mean)			
Change to subjects' costs	**Cases** (n = 657 243)	**Controls** (n = 2 628 972)	**Difference (95% CI)**	**p-value*** ($d_{Cohen's}$)
Total Primary care				
Case 25% Control 125%	1382.69 (1.56)	1401.68 (1.51)	-18.99 (-23.23 - -14.74)	<.001 (0.01)
Case 50% Control 150%	2765.38 (3.11)	1682.02 (1.81)	1083.37 (1076.32 – 1090.42)	<.001 (0.42)
Case 75% Control 175%	4148.08 (4.67)	1962.35 (2.11)	2185.72 (2175.69 – 2195.76)	<.001 (0.59)
Case 50% Control 125%	2765.38 (3.11)	1401.68 (1.51)	1363.71 (1356.93 – 1370.48)	<.001 (0.54)
Case 75% Control 150%	4148.08 (4.67)	1682.02 (1.81)	2466.06 (2456.25 – 2475/88)	<.001 (0.68)
Case 25% Control 175%	1382.69 (1.56)	1962.35 (2.11)	-579.66 (-584.80 - -574.52)	<.001 (-0.31)
Total Secondary Care				
Case 25% Control 125%	2285.63 (7.31)	10011.33 (20.34)	-7725.69 (-7768 - -7683.33)	<.001 (-0.49)
Case 50% Control 150%	4571.27 (14.62)	12013.59 (24.41)	-7442.33 (-7498.09 - -7386.56)	<.001 (-0.36)
Case 75% Control 175%	6856.90 (21.93)	14015.86 (28.48)	-7158.96 (-7229.41 - -7088.51)	<.001 (-0.28)
Case 50% Control 125%	4571.27 (14.62)	10011.33 (20.34)	-5540.06 (-5489.16 - -5390.96)	<.001 (-0.30)
Case 75% Control 150%	6856.90 (21.93)	12013.59 (24.41)	-5156.69 (-5221.01 - -5092.37)	<.001 (-0.22)
Case 25% Control 175%	2285.63 (7.31)	14015.86 (28.48)	-11730.22 (-11787.85 - -11672.60)	<.001 (-0.55)
Total costs				
Case 25% Control 125%	4113.34 (8.27)	12196.59 (20.96)	-8083.25 (-8127.41 - -8039.09)	<.001 (-0.50)

Case 50% Control 150%	8226.68 (16.54)	14635.91 (25.15)	-6409.23 (-6468.23 - -6350.23)	<.001 (-0.29)
Case 75% Control 175%	12340.01 (24.81)	17075.22 (29.34)	-4735.21 (-4810.52 - -4659.90)	<.001 (-0.17)
Case 50% Control 125%	8226.68 (16.54)	12196.59 (20.96)	-3969.91 (-4022.24 - -3917.59)	<.001 (-0.21)
Case 75% Control 150%	12340.01 (24.81)	14635.91 (25.15)	-2295.89 (-2365.13 - -2226.65)	<.001 (-0.09)
Case 25% Control 175%	4113.34 (8.27)	17075.22 (29.34)	-12961.89 (-13021.65 - -12902.14)	<.001 (-0.60)

*p-value calculated from t-test (case-control), <0.05 = significant Holm-Bonferroni confirmed it was correct to reject the null hypothesis

7.11 Discussion

7.11.1 Summary and reflections on findings

People with pain-related diagnoses and receiving prescriptions for opioids accessed significantly more healthcare resources than those with similar diagnoses but not prescribed opioids from primary care. Increased healthcare resource utilisation and consequent costs were associated with female gender, higher levels of deprivation and prescribing persistence of six months or more.

The results demonstrated primary care bore the major burden of increased healthcare utilisation by those receiving opioid prescriptions. General practice remains the first port of call and gatekeeper of the rest of NHS access (Loudon 2008; Greenfield et al. 2016), so it is not surprising the majority of transactions take place in that sector. There is a link between primary care and ED attendance, noted by the small reduction in the percentage variance predicted in the regression models, when ED attendance was removed from the model. The obvious explanation is that increased ED attendance is indicative of greater incidence of illness, health concerns or difficulty coping with the same. ED attendance was a greater predictor of primary care interaction than gender in the regression model (Table 7.7), which might fit with that understanding.

Regression modelling was not very reliable for predicting attendance or admission to secondary care services. This is likely reflective of the complexity of decision making leading to referral or the decision of an individual to go to ED if for anything other than a genuine medical emergency, for example. Reasons for attending or referral were not available to this study and therefore, only postulations of cause can be made. People using opioids for long-term pain conditions may have greater health concerns or anxiety attached to their condition, leading them to seek support. The use of opioids may cause additional health problems leading to secondary care healthcare utilisation.

Greater healthcare utilisation by women compared to their male counterparts, in case and control groups, was a probable outcome given the prescribing trends noted in Phase 1 of the study (Section 3.5.3, Section 4.5.2 and Section 5.5.3) and

the results of the regressions described (Table 7.7). Less expected was the degree of difference between case and control subjects. Whilst in primary care some of this variance might be accounted for by issued prescriptions being counted as an interaction, the reasons for the differences in outpatient attendance and inpatient admission require more investigation. Given the known adverse effects of opioids, it is not unreasonable to suspect that some increase in attendance is due to that, whether or not they are identified. It is difficult to make any definitive statement about possible causation without knowing reasons for attendance, but it is worthy of further investigation.

Similarly, equal rates of attendance at ED by male and female case subjects was an interesting finding, especially as there were gender differences in the control group. It is understood women present more frequently to healthcare services and they report pain more frequently than men (Rhudy and Williams 2005; Zhang et al. 2021). It is unlikely this alone would be sufficient explanation to account for the differences in secondary care interactions. However, more frequent primary care attendance is perhaps likely to result in more out-patient appointments. Primary care practitioners refer for specialist opinion and treatment of serious pathology or when they have exhausted treatment and support options (Ringberg et al. 2014; Tzartzas et al. 2019). As previously discussed, (Section 3.6.5 and Section 4.6.3), women report difficulty accessing treatment and support for painful conditions, especially those unique to females (Williams 2021). Further research to investigate differences in the outcome of appointments, between genders would be helpful. For example, examining whether there are gender differences in the proportion of primary care appointments that result in referral for specialist opinion.

Differences in healthcare utilisation based on age-group were heavily weighted towards case subjects in all aspects other than LoS. People under 65 years old, receiving opioid prescriptions had more hospital admissions than their control group and longer LoS per admission. Whilst older opioid users had more admissions than their controls, their admissions were on average shorter.

Reasons for admission in the different groups were not available for this study. It would be valuable to determine how differences in LoS were linked to opioid prescribing. Younger patients accessing acute care services may perhaps be expected to be more unwell than their control subjects who, whilst having similar conditions, were not using opioid analgesics. Being unwell, may take longer to resolve, leading to greater LoS. In older people, admission could sometimes be due to opioid-induced effects which might be more quickly resolved in an acute care setting (e.g., constipation, sedation). However, whilst this may account for LoS, it does not easily explain the differences in out-patient or ED attendance that were also noted.

Receiving opioid prescriptions for 6 months or more was the strongest predictor for increased healthcare utilisation and consequently, costs in all sectors (Section 7.9). If each prescription issue was counted as an appointment in primary care, this may have skewed the model in favour of the variable. However, receipt of any opioid prescription was also a positive predictor of attendance. Significant differences in utilisation and consequent healthcare costs were demonstrated between groups of less than and more than six months prescription persistence. Duration of opioid use has been previously shown to be connected to adverse effects (Cohen et al. 2008; Mundkur et al. 2017; Bialas et al. 2020) and this would likely necessitate additional healthcare input. People requiring long-term prescribing of opioids may reasonably be presumed to be in worse health than those not receiving opioids despite having similar diagnoses. However, the evidence to use opioids in the conditions highlighted in this study is not supportive (Els et al. 2017; Faculty of Pain Medicine 2021). TOPAS affirms a link between prescribing persistence and healthcare use, even if the nature of the connection cannot be fathomed at this stage.

Stratification of utilisation and costs by deprivation showed some interesting patterns. Empirically, differences between quintiles in either case or control subject groups did not appear particularly large. Differences between groups were statistically significant for every measure, however. Regression analysis

suggested greater deprivation was a better predictor of healthcare utilisation than lower deprivation. Perhaps notable is that healthcare utilisation in the least deprived quintiles was not as different to the most deprived as might have been expected. ADE data was not extensive, but there was a clear difference between case and control quintiles. ADEs of opioids often present as other health conditions or the potentiation of existing poor health. It is possible that too often, the contribution of opioids to the individual's presentation is missed as a result.

Prescribing trends described in Phase 1 of this study noted prescribing in WIMD5 areas had a larger percentage increase than WIMD1 areas during the study (Chapter 4). The gap in prescribing rates of strong opioids especially was narrowing towards the end of the study period and the implications for population health must be considered. Are the limited differences and increase in prescribing, an indication that the prevalence of pain is increasing in all sections of the Welsh population? If so, does the increase in opioid prescribing and subsequent increased use of healthcare services indicate a failure to provide timely and effective support to people living with painful conditions?

People living in less deprived areas would likely be considered to have easier access to services in most cases. A greater percentage may be able to self-fund pain management support or alternative treatments than their counterparts in more deprived areas. Despite that, opioid prescribing continued to increase, and more healthcare interactions occurred over the eleven years of the study.

The simplest explanation for the differences between case and control subjects noted in this study would be that people are receiving opioids because their condition is worse or more difficult to treat than their comparator's. However, this is likely a massive oversimplification. With the evidence of the harms of opioids growing all the time, opioid analgesics are no longer recommended for a number of the conditions examined in this study such as back pain (National Institute for Health and Care Excellence 2016), neuropathic pain (Centre for

Clinical Practice at NICE 2013) and chronic primary pain (National Institute for Health and Care Excellence 2021), particularly for long-term use.

The concern is that without taking any action to change opioid prescribing, Wales could end up having an even greater percentage of the population harmed by opioids than might be implied by the data presented here. Certainly, the evidence does not support the notion that opioids are leading to improvement (Harrison and Cormack 2018; All Wales Medicines Strategy Group 2021).

7.11.1.1 Comparison with other literature

No previous studies from the UK, examining the association between opioid prescribing for chronic pain and healthcare utilisation were found. However, increased healthcare utilisation following the initiation of opioids has been reported across the world (Kern et al. 2015).

Chang and colleagues (2018) examined healthcare utilisation in American people deemed to be receiving 'high risk' prescription opioid use in 2012 (Chang et al. 2018). The study examined data from nearly 900,000 people, of whom just over 21% had received an opioid prescription. Comparisons were made between all people included in the study, including those receiving opioids and the specified user groups rather than as a case-controlled study (Chang et al. 2018). Total healthcare utilisation was examined by cost rather than attendances but were approximately twice as high in the opioid user group as the combined group's total across the study period.

Kern and colleagues (2015) conducted an analysis of healthcare resource utilisation by opioid users in the USA (Kern et al. 2015). Unlike this study, the comparisons made were between acute and chronic opioid use, rather than a case-control study. The Kern study looked at office visits (near equivalent to primary care in the UK), outpatient visits, inpatient admissions and length of stay. They observed an increase in all variables in the six months following opioid initiation, the largest percentage increases noted in people with weak opioids

(Kern et al. 2015). After the initial large increase in healthcare utilisation, levels of use started to decline although did not return to pre-opioid levels after a further six months (Kern et al. 2015). Therefore, as seen in this study, extended prescription of opioids resulted in greater healthcare utilisation.

It is difficult to compare costs between the US and UK due to differences in healthcare systems and how tariffs are determined. The increased healthcare utilisation and associated costs demonstrated in this study are, however, consistent with the findings of other studies (Kern et al. 2015; Kay et al. 2017)**.** Chang's study (2018) supports the TOPAS findings that there is a correlation between prescription opioid use, increased healthcare utilisation and, consequently, costs.

7.11.1.2 Acute care

Chang et al. demonstrated hospitalisation was three times higher in those receiving opioids than the combined group (9.28% versus 2.98% respectively) in 2012, when opioids were first prescribed (Chang et al. 2018). In this study, healthcare utilisation was examined during the whole period that opioids were being prescribed. Hospital admission was twice as frequent in opioid users in TOPAS case subjects as controls. Different measures were examined in the two studies, but the findings are mutually supportive. Both suggest people using prescription opioids are more likely to be hospitalised for any cause than people not using those medicines (Chang et al. 2018). Opioid users who undergo inpatient surgery have been shown to have an increased likelihood of further hospitalisations than nonopioid users. In a group of commercially insured patients for example, 17% of those prescribed opioids after one surgery had subsequent admissions compared to 12% who did not (Brummett et al. 2019).

A study from Germany observed a significant increase in outpatient consultations, following the initiation of opioids. As with other studies, the increase in resource utilisation did not persist, even when opioids continued (Bruggenjurgen et al. 2007). The study stratified results by drug and noted

fentanyl was associated with additional resource utilisation compared to oxycodone and morphine (Bruggenjurgen et al. 2007).

7.11.1.3 Emergency department utilisation

Attendance at emergency departments was significantly more common by people receiving opioid medicines than control subjects. Data on reasons for attendance was not complete on extraction from the databank, so was not explored in this study. However, the National Pain Audit (2012) collated responses from people using chronic pain services across the UK in regard to healthcare utilisation. Twenty percent of respondents stated they had attended the emergency department in the previous six months, specifically looking for help with pain (Price et al. 2012).

Literature comparing ED attendance in people prescribed opioids with controls from the UK was not found. Braden et al. analysed emergency department attendance by people, receiving opioid prescriptions for 90 days or more, under one of two insurance schemes (federal and private), for non-cancer pain (Braden et al. 2010). Women composed 72% of Medicaid patients and 59% of privately insured people, with the average 62%, slightly higher than noted in this study. The most common painful diagnosis was back pain, present in around 40% of cases. Emergency department visits were recorded in 25% of study participants, with an average of 0.8 attendances per person during a twelve-month study period. Greater numbers of ED visits were not correlated to dose or over 6-month duration of use, unlike to what was noted in TOPAS (Braden et al. 2010). Increased visits to ED were associated however, with the receipt of more than one form of opioid medicine, e.g., modified release and standard release and the additional use of benzodiazepines (Braden et al. 2010).

Whilst polypharmacy was not examined in this study, the use of combinations of medicines have been an increasing cause of concern in the UK, due to higher risk of harm, dependence, and death (Torrance et al. 2018; Taylor et al. 2019). Of 9,940 people receiving 3 or more opioid prescriptions within 90 days, 51 suffered

overdose and 6 died (Dunn et al. 2010). The risk of overdose increased with rising dose. Estimations suggest a 1.8% annual overdose risk for people receiving opioid doses of 100mg OMEQ and above (Dunn et al. 2010).

7.11.1.4 Prescription persistence and dose

Kern et al. (2015) defined chronic opioid use as 183 or more days, and with repeated prescriptions filled within 30 days of the previous one (Kern et al. 2015), which was the same as the definition used in this study. Primary care visits and other outpatient-type appointments were noted to increase by 3 and 5 times, respectively in the first six months of treatment (Kern et al. 2015). After 6 months of opioid treatment, utilisation and costs reduced significantly with the largest reduction observed for in-patient admissions.

The use of opioids was associated with greater healthcare utilisation in another American study (Kay et al. 2017). Doses of greater than 200mg OMEQ were not associated with a higher number of ED visits or clinic visits than people receiving lower daily doses, however. Interestingly more calls to out of hours services were made by people prescribed the highest OMEQ doses compared to lower doses (Kay et al. 2017). These results differed from Chang et al. (2018), who defined chronic opioid use as receiving 100mg OMEQ per day for more than 90 consecutive days (Chang et al. 2018) and demonstrated chronic use as defined was associated with twice as much healthcare use compared to people on lower doses or no opioid. Even higher use of healthcare resources was observed when opioids were combined with other high-risk medicines such as benzodiazepines or in the presence of opioid misuse disorder (Chang et al. 2018). Prescribing persistence was shown to be lengthier in the areas of Wales with highest levels of deprivation (Section 3.5.5). Increased deprivation was also correlated to greater healthcare utilisation and consequent costs.

7.11.1.5 Comparisons of costs

Studies examining costs associated with opioid analgesics are generally focussed on adverse effects or misuse, rather than whether use results in additional

healthcare problems. In Wales, the cost of medicines classified as opioid analgesics (not including co-products such as co-codamol) in the BNF (BNF: British National Formulary - NICE. 2021) increased 46.3% from £10.4 million in the year 2004-2005 to £19.2 million in 2014-2015, totalling £177.7 million over the TOPAS study period (Welsh Government 2021). Opioid analgesic costs peaked in 2015-2016 and have reduced each year since, reflecting the small reduction in prescription numbers reported (Section 6.5) and falling costs of some medicines as they come off patent or Welsh contracts are negotiated. Prescribing accounts for around one-third of primary care spending (Auditor General for Wales 2018) in Wales. Health boards spent £1.39 billion on primary care services in 2016-2017, a 5% reduction in real terms from 2010-2011 when figures were previously reported (Shared Services Partnership 2021). Overall, health board spending in 2016-2017 was recorded as £6.32 billion, so primary care accounted for 22% of the total (Auditor General for Wales 2018). Based on the calculations used for this study, the cost of healthcare use for people living with the six major chronic pain types is upwards of £1.3 billion per year in Wales. This is the first estimate of healthcare costs for this patient group to be made in the country.

Kern and colleagues (2015) calculated the average all-cause costs which more than doubled (from $13,459 to $31,695) in the first six months of opioid treatment (Kern et al. 2015). Whilst there was a reduction in overall costs after six months for chronic opioid users, they did not return to pre-opioid levels. A difference was noted for in-patient stays, however, where a return to below pre-treatment costs was noted after six months (Kern et al. 2015). This was an interesting finding in light of the results from this study, where in-patient length of stay and subsequently cost per admission was, on average, lower for people prescribed opioids than not. However, prescribing persistence greater than six months was associated with a much higher number of admissions, length of stay and therefore, overall associated costs than those with shorter duration of prescribing or none at all.

The cost of back pain to the UK economy is often quoted as £12 billion per year, although that estimate is now 20 years old (Maniadakis and Gray 2000). Healthcare costs, excluding medicines, comparable to those used in this study were estimated to be £974 million by Maniadakis and Gray (Maniadakis and Gray 2000). This demonstrates the healthcare costs of back pain and, in fact, all chronic pain conditions, are relatively small relative to the overall economic impact (Phillips 2008).

Studies which have examined the cost-effectiveness of using opioid analgesics from the perspective of only healthcare utilisation are rare. However, studies comparing the cost-effectiveness of opioid analgesics to other treatment strategies have been conducted. Takura et al. (2021) used a Markov model to calculate the incremental cost-effectiveness ratio (ICER) for people with hip or knee osteoarthritis (OA) and who received either opioids such as codeine or tramadol or non-opioid strategies including surgery or other medicines such as non-steroidal anti-inflammatory drugs, paracetamol or steroids, in line with treatment guidelines used in Japan (Takura et al. 2021). In people eligible for surgery, non-opioid treatment strategies had higher efficacy and were less expensive. QALYs for the knee OA, non-opioid group were 11.53 compared to 11.50 for the opioid group over 30 years (Takura et al. 2021). The analysis suggested that opioids were dominated for both hip and knee OA, leading the authors to conclude that non-opioid strategies were cost-effective compared to opioids for surgery-eligible patients with knee or hip OA (Takura et al. 2021). These conclusions concurred with those of Katz et al. (2016) who demonstrated regimens including tramadol were dominated by those using ibuprofen or naproxen (Katz et al. 2016). Also, Smith et al. (2017) observed that people who received tramadol or tramadol followed by oxycodone for knee OA had surgery delayed for seven or nine years, respectively. However, both opioid-containing strategies increased costs and decreased QALYs compared to opioid sparing regimens (Smith et al. 2017).

A UK study examined the cost-effectiveness of tapentadol compared to oxycodone for people with chronic pain who had not responded to or could not tolerate morphine (Ikenberg et al. 2012). Over one-year or thirteen 4-week cycles of Markov model, tapentadol was associated with fewer health care visits and additional medicines for managing side-effects than oxycodone. However, the difference in QALYs between tapentadol (0.6371) and oxycodone (0.6237) was small. A second UK study undertook a cost-utility analysis using a cohort model to calculate cost differences between two oxycodone products, one including naloxone and designed to reduce the incidence of opioid-induced constipation. The 12-week study period generated a ICER of £5,841.56 per QALY for the naloxone containing product (Dunlop et al. 2012). The model demonstrated a reduction in healthcare resource use such as primary care visits in addition to fewer prescriptions for laxatives when the oxycodone-naloxone product was used. Quality of life gains were suggested by the authors, although differences were not demonstrated to be statistically significant (at week twelve, adjusted means were 0.5029 compared to 0.4640, p=.0185 for the oxycodone/naloxone group and oxycodone group, respectively) (Dunlop et al. 2012). Whilst these studies, both run by the pharmaceutical companies marketing the medicines being trialled, demonstrated cost-effectiveness of different opioid analgesics or differences in healthcare use and associated costs, none examine specifically the difference in utilisation in the same way as the TOPAS study has attempted. Further research is warranted to examine, in detail, the impact of opioid prescribing for non-cancer pain on healthcare utilisation with a focus on less commonly studied adverse effects such as depression and anxiety or illness resulting from reduced immunity.

7.11.1.6 Healthcare use associated with pain, opioid analgesics, and demographic factors

Chronic pain is a difficult condition to manage and to definitively diagnose (National Institute for Health and Care Excellence 2021). The general perception of pain is that it is connected to an underlying problem, injury or illness (Section 1.3). Therefore, it perhaps makes sense from a clinical perspective to see more

healthcare attendances by people using opioids, as it could be assumed they are experiencing more difficult symptoms than their study controls (McGorm et al. 2010; Johnston 2019; Tzartzas et al. 2019).

Whilst there is limited literature on the impact of opioids per se on healthcare utilisation, reasons for frequent attendance across sectors has been examined (Neal et al. 1998; McGorm et al. 2010; Ringberg et al. 2014; Patel et al. 2015; Welzel et al. 2017; Tzartzas et al. 2019). It has been estimated that 15% of primary care attendances are made by 3% of patients (Neal et al. 1998). Characteristics of frequent attenders appears to vary depending on the setting (Neal et al. 1998; Byrne et al. 2003; Hunt et al. 2006) and the conditions they are seeking support for (Menchetti et al. 2009; Lewer et al. 2020). Primary care frequent attenders are considered more likely to be female and attendance appears to increase with age (Neal et al. 1998; Welzel et al. 2017), which corroborates the findings of primary care attenders in TOPAS (Section 7.8.1). The contribution of chronic pain to presentation in primary care has also been observed to result in twice as many visits compared to non-pain related attendances with men and women almost equally represented (Mann et al. 2016).

Characteristics of frequent ED attenders appear different to those in other sectors (Byrne et al. 2003; Hunt et al. 2006; Greenfield et al. 2020). The most recent study of ED attendances in the UK demonstrated that 10% of people were frequent attenders and accounted for 25% of ED visits (Greenfield et al. 2020). Whilst that study did not discuss gender characteristics, others have revealed that men are likely to attend ED more frequently than women, and that attendance increased with age and was more common in people who lived alone (Hull et al. 1998; Byrne et al. 2003; Moore et al. 2009). A study of ED attendance, with pain as a driver for attendance had a similar gender split to this study, with 52% of attendees being male (Daniels et al. 2017), although attendance declined with age in that case. In line with previous studies, men in the control group of this study had more ED attendances than their female counterparts.

Frequent ED attendance has been noted to be connected to recurrent presentation to primary care (Hull et al. 1998; Moore et al. 2009). This would fit with the results of the linear regression (Section 7.9.1), which showed a correlation between GP visits and ED attendance. Even in healthcare systems where insurance costs are incurred, greater attendance for emergency care has been linked to frequent attendance with family doctors (Byrne et al. 2003; Hunt et al. 2006). A 2012 study of secondary care healthcare use in England revealed around twice as many ED attendances in the most deprived deciles compared to the least. Further, deprivation was associated with lower conversion to hospital admission. This implies that ED attendance by people from more deprived deciles was more likely due to minor health problems (McCormick et al. 2012). Living in areas of higher socio-economic deprivation and having long-term health conditions have also been noted as predictors for more frequent attendance at ED (Scantlebury et al. 2015; Giebel et al. 2019). It appears perhaps that whilst there is greater health need in areas of socioeconomic deprivation, there is also more inappropriate use of services. Scantlebury et al.'s (2015) study noted 73.6% of subjects in the 90th centile (less deprived) reported knowing how to contact out of hours primary care services (OOH) compared to 48% in the 10th centile. It is not surprising therefore, that even minor health issues arising outside of normal working hours, might result in a visit to ED.

Referrals to secondary care were not fully coded for in this study (Section 8.6), although from the data available, case subjects received more and also more tests and radiology contacts (Section 7.8.1). Referrals into secondary care have been associated with less experienced doctors (Tzartzas et al. 2019), female primary care doctors (Ringberg et al. 2013), and previous experience or familiarity with the specialist being referred to (Kinchen 2004). More referrals were observed from ED for people from areas of higher deprivation (McCormick et al. 2012). It has been demonstrated, however, that deprivation is associated with lower rates of attendance and cancellation of booked appointments but increased likelihood of attending emergency departments (McCormick et al. 2012). This is potentially important as healthcare services of most benefit to

people living with pain or using opioid analgesics are generally provided as out-patient clinics and require multiple attendances over extended durations.

An Australian study examined health service utilisation by 1,243 people living with chronic pain (Nielsen et al. 2016), specifically looking at the use of non-opioid pain treatments by people also using opioids. There was use of complementary and alternative medicines and specialist pain treatments by participants in all groups. However, the likelihood of accessing them was linked to the ability to pay or having insurance policies that covered it (Nielsen et al. 2016). As all participants were in receipt of opioid medicines, those who were unemployed or did not or could not have inclusive insurance policies, were more likely to have only opioids or other medicines to manage their pain (Nielsen et al. 2016). A partly insurance-based healthcare system is an additional barrier noted in the Australian study, rather than the only barrier considered to prevent people using alternatives to opioids (Nielsen et al. 2016). Remuneration for services including physiotherapy and psychology is problematic in countries where health insurers dominate decision making (Finestone et al. 2016). The NHS in Wales and the rest of the UK, reduces ability to pay as a cause of non-attendance or accessing some supportive services. Alternative therapies, which people with pain might want to access are still subject to payment however, thus introducing barriers for people with limited funds.

In the UK, pain management clinics are commissioned by CCGs or operated by Health Boards and, based on standards set by the Faculty of Pain Management should provide access to evidence-based, multi-disciplinary support (Faculty of Pain Medicine 2021). Price (2019) sets out the development of pain services in the UK, which has been heavily criticised by a number of different Government reports over the years (Price 2019). Since 2008, when the Chief Medical Officer's reports focussed on chronic pain (Chief Medical Officer of England 2009), more focus has been paid to pain management and service development. The approach taken in Scotland is set out in Section 8.4.2. The National Pain Audit (2012) highlighted that gaps remained in services throughout the UK (Price et al.

2012). Services in Wales did not fully participate with the audit and consequently, were not able to be benchmarked against the outcomes examined (Price et al. 2012). Only 40% of services were shown to operate multi-disciplinary services. The audit did not examine service provision based on socioeconomic deprivation, despite the overwhelming evidence that chronic pain is disproportionately associated with deprivation (Engel 1959; Saariaho et al. 2011; Newman et al. 2017; Gulliford 2020). Future reviews of service provision would benefit from examining not just the make-up of services but also their accessibility to different patient groups. This is especially important given the higher rates of opioid analgesic prescribing in more deprived areas demonstrated in this study (Chapter 4 and Section 5.5.4) and by others (Mordecai et al. 2018; Torrance et al. 2018; Chen et al. 2019) and the harms associated (Chapter 4).

7.12 Conclusion

There was a clear association between the receipt of prescription opioids and healthcare utilisation. Increased healthcare utilisation was associated with female gender, age 65 years and over, living in more socio-economically deprived areas and receiving opioid medications for more than 6 months. Length of hospital admission was the only variable where receiving opioids appeared to have a negative association, although opioid use was associated with more hospital admissions than control subjects.

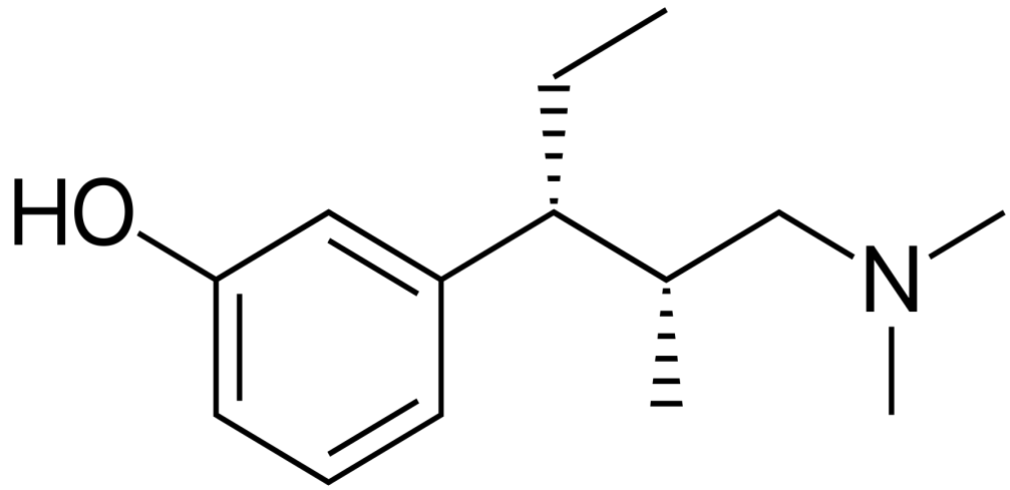
The costs of healthcare utilisation were clearly greater in people receiving opioids, with an average annual cost of just under £1billion, based on the variables used in this study. Whilst not inclusive, this conservative estimate is the first to be made for healthcare costs linked to opioid use in Wales. All study subjects had recorded pain-related diagnoses and varied only by the receipt of opioid prescription. This study has also provided the first estimation of annual healthcare costs associated with six major pain-related diagnoses in Wales, namely osteoarthritis, rheumatoid arthritis, back pain, neck pain, fibromyalgia, and neuropathic pain. The estimation of 1.3 billion per year is near equivalent to

the total primary care spend in Wales, which perhaps puts into perspective the overall burden that pain places upon the NHS.

Further analysis is needed to determine more accurately if there are differences in the services accessed by people prescribed opioids compared to non-users. Moreover, investigation whether differences are associated with particular opioid medicines or duration of use is warranted. As the evidence to support the use of opioids for long-term conditions weakens, there has been some reduction in prescribing. However, as discussed elsewhere in this thesis (Section 4.6), evidence suggests that people who are most susceptible to the harms of opioids, are more likely to be receiving them, at higher doses and for prolonged periods of time. The same factors were also associated with increased healthcare utilisation and consequent costs, which could be an indication of harm.

Policy makers and healthcare leaders will need to reconsider the reasons for opioid prescribing, particularly that which continues for extended periods and may be causative for other health concerns, from the perspective of patients and practitioners. It appears the cost of opioid prescribing to NHS Wales could be significant and related more to harms than help. Defining who is likely to benefit from opioid treatment without inflicting greater damage and who and where other options need to be provided and promoted, is emerging as a necessary next step. It is hoped this work is a useful contribution to improving and preserving the health and wellbeing of the people of Wales. It illustrates the need to urgently address health inequalities, iatrogenic harm and to ensure the best use of fragile NHS resources.

Chapter 8
Discussion



"'Finished last' will always be better than 'did not finish' which always trumps 'did not start'"
Anon

Chapter 8 – Discussion

8.1 Chapter overview

This thesis sought to examine how opioid analgesic prescribing had changed over time in Wales and whether factors such as gender, age or socioeconomic status affected it. Further, the influence of guidelines and legislation on opioid prescribing and ultimately, how opioid prescribing might be associated with healthcare service use and its associated costs was examined.

The research objectives were:

1. To examine prescribing trends of opioid analgesics between 2005 and 20015 and scrutinise whether trends differ between gender or different age-groups (Phase 1 - Chapter 3)
2. To determine if opioid analgesic prescribing trends are affected by socioeconomic deprivation status (Phase 1 - Chapter 4)
3. To analyse trends in oral morphine equivalent doses and prescribing duration using estimated measures for each (Phase 1 - Chapter 5)
4. To determine if general opioid prescribing trends appear affected by legislative or clinical guidance changes during the study period using time series analysis (Phase 1 - Chapter 6)
5. To assess the frequency of primary and secondary healthcare attendance by patients with defined non-cancer pain conditions receiving opioid analgesic therapy (Phase 2 - Chapter 7)
6. To estimate healthcare service costs associated with the use of opioid analgesics (Phase 2 - Chapter 7)

This final chapter now seeks to draw together the threads from those that have gone before, to discuss factors of influence not previously covered and to set out the potential future direction of health care policy to address opioid prescribing and pain management more generally, in Wales.

8.2 Summary of study results

The results of this study demonstrate large increases in prescribing of all opioid analgesics (Section 3.5.1), but especially of strong opioids such as morphine, oxycodone and fentanyl, which place a disproportionate burden on the population (Chapter 5). The highest levels of prescribing and consequent opioid burden were observed in the most socioeconomically deprived areas of Wales (Chapter 4 and Section 5.5.4) which, has implications for the overall health and wellbeing of those communities. Women received around 50% more prescriptions than men between 2005 and 2015 (Section 3.5.3), although there were signals that men may receive higher doses of opioids per prescription (Section 5.5.3.2). National prescribing indicators appeared to have a small effect on prescribing trends but legislation less so (Chapter 6).

People receiving prescriptions for opioid analgesics had 5 times more attendances in Primary Care (Section7.8.1), around 3 times as many out-patient (Section 7.8.2) and emergency department visits (Section 7.8.3) and twice as many in-patient attendances (Section 7.8.4) as those with similar pain-related diagnoses but who did not take opioid analgesics. Higher rates of attendance led to significantly higher healthcare costs associated with opioid analgesic use, compared to control subjects (Section 7.10.1).

Concerns about increasing rates of opioid prescribing in Wales have been borne out by this research. In particular, the use of large, linked datasets are an important tool in monitoring prescribing trends and allow targeted analyses of demographic groups who may be at greater risk of harm from changes in opioid prescribing. The TOPAS study demonstrates that expanding on the relatively simplistic view provided by standard dispensing data available to Health Board Medicines Management teams and national organisations setting prescribing policy, will be important in addressing the high rates of opioid prescribing that continue in Wales and reducing variation within the population. Means of accessing the kind of detailed data used in this study, in a more straightforward

and timely manner need to be invested in, to improve the effectiveness of interventions made in practise.

The increases in prescribing rates were not necessarily unexpected, given previous prescribing data (All Wales Medicines Strategy Group 2013). Examination by different demographic categories has, however, brought issues into focus which have not been so widely discussed in Wales in relation to prescribing or addressed in initiatives aimed at changing prescribing habits (Welsh Government 2020; All Wales Therapeutics and Toxicology Centre 2021). Disproportionate prescribing to women and in areas of greatest deprivation are clearly issues that need to be addressed. Studies from other areas of the UK have also shown these disparities (Macfarlane et al. 2009; Zin et al. 2014; Ruscitto et al. 2015; Bedson et al. 2016; Mordecai et al. 2018; Todd et al. 2018; Torrance et al. 2018; Macfarlane et al. 2020).

Higher prevalence of pain, and consequently opioid prescribing, in women is acknowledged (Dao and LeResche 2000; Rhudy and Williams 2005; Pieretti et al. 2016), even if the reasons for it are less well understood (Terplan 2017; Mazure and Fiellin 2018). Higher levels of ill-health or pain in areas of greater socioeconomic deprivation are often used as the explanation for higher rates of opioid prescribing (Todd et al. 2018; Nowakowska et al. 2020; Schifanella et al. 2020) whilst acknowledging that this alone is not justification enough. Of particular concern is the harms of opioids medicines are likely to have greater impact in those areas where health is already worse.

Little data is available in Wales regarding specialist pain service access or how that might vary in areas of different socioeconomic deprivation. When the demographics of people accessing a chronic pain service in Glasgow were examined, it was notable that a higher proportion of attendees came from wealthier areas (Moore et al. 2020). People from less affluent areas of the city were less likely to attend the initial assessment and attended fewer sessions once accepted to the service. Given pain reporting appears to correlate with

deprivation, this was surprising. The authors suggest multiple factors are likely to account for the difference, including poorer support seeking behaviour in people more socioeconomically deprived, lower referral rates from areas of higher deprivation and poor health activation (Moore et al. 2020).

8.3 Why are opioids prescribed?

Over the study period (2005 to 2015), evidence that opioids have poor effect for most people using them, particularly in chronic pain conditions, continued to emerge (Trescot et al. 2008; Els et al. 2017; Stannard 2018a). This begs the question of why opioids continue to be prescribed, when so much is known about the harms (Baldini et al. 2012; Blanch et al. 2014; Els et al. 2017; Salas et al. 2020) and limited benefit in reducing pain or improving function (Baldini et al. 2012; Krebs et al. 2018; Richards et al. 2018).

8.3.1 Waiting for help

Prescribing opioids has been suggested to be a surrogate for access to alternative pain management support (Finestone et al. 2016). Pain service provision in Wales was not mapped as part of this study but the National Pain Audit (2012) collected data demonstrating every health board in Wales had chronic pain service provision, with 80% claiming to have multi-disciplinary teams (Price et al. 2012). Average waiting time for these services at the time of the audit was 33 weeks (Price et al. 2012). Official figures on waiting times for pain services were not available during the composition of this thesis.

The impact of long waiting times on the people waiting was examined by the Community Health Councils of Wales (CHC) (Board of Community Health Councils in Wales 2018). It was acknowledged that being in pain whilst awaiting orthopaedic and other types of surgery was problematic, especially as some pain services do not see people on waiting lists for interventions from other specialities (Board of Community Health Councils in Wales 2018). People responding to the CHC consultation revealed concerns about continuing 'strong painkillers' due to worries "*about side-effects, over reliance and reduced*

effectiveness." The report went on to highlight delays to surgery were coupled with "*long waiting times for pain management clinics, up to 2 years in some cases*." (Board of Community Health Councils in Wales 2018).

IASP gave recommendations on waiting times for pain services globally in 2011, with a suggested 8 weeks for persistent long-term pain without significant progression (Collett et al. 2011). A systematic review of the effects on people waiting for chronic pain treatment suggested that waiting for six months led to significant deterioration in health-related quality of life and psychological wellbeing (Lynch et al. 2008). An investigation by the Pharmaceutical Journal (2020) requested data directly from pain service providers and found waiting times ranged from 6 to 111 weeks, with the longest waits in Wales (Connelly 2020).

During the Covid-19 pandemic, many specialist services, including pain services, were temporarily suspended. Most English pain services reported continuation of some pain physician work direct to patients. However, the range of services available, inevitably reduced (Faculty of Pain Medicine 2020). No equivalent data for Wales was found. The Faculty of Pain Management (FPM) gave guidance to its members (anaesthetists) in relation to returning services post-pandemic (Faculty of Pain Medicine 2020). Whilst understandably the focus of advice was on prioritising workload and stratification processes for people referred, there appeared to be no consideration of the impact of changing services on people waiting and colleagues working in Primary Care (Faculty of Pain Medicine 2020). It may be assumed that people who are unable to access specialist interventions will more likely access whatever services are available.

Primary Care, unlike Acute, Secondary or Tertiary services, does not have the option of discharging people. Primary Care has to continue to offer support and treatment to people, even if they are waiting for or receiving input from specialist providers. This may lead to GPs and other practitioners in primary care resorting to prescribing or maintaining opioid prescribing in the face of poor

outcomes, simply because they feel they have nothing else to offer (Finestone et al. 2016). McCrorie et al. (2015) support this notion, with GPs explaining during interviews that continuing to prescribe opioids was often due to long waits for other treatments or support, or patients not being ready to consider alternatives to medicines (McCrorie et al. 2015).

An examination of routinely collected longitudinal data from primary care practices in England noted increasing numbers of primary care appointments were more likely to result in the prescription of a strong opioid. An odds ratio of 3.04 (range 2.48 – 3.73) was observed for more than 12 visits per year (Foy et al. 2016). Increased attendance has been associated with greater self-perceived ill-health and the need for support (Neal et al. 1998; Morriss et al. 2012; Daniels et al. 2017) (Section 7.11). So, it is perhaps understandable that, in the absence of acceptable or timely alternatives and when people present with increasing need for support, prescribing becomes an acceptable option to all parties.

However, there is some evidence that even once seen by 'specialists', opioid prescribing remains a frequent intervention. Foy et al.'s study (2016) demonstrated referral to chronic pain services also resulted in an increased likelihood of strong opioid prescribing that was then likely to persist (OR 5.74, range 5.09-6.47) (Foy et al. 2016). McCrorie's study (2015) reported a GP statement, *"...every time I send somebody to chronic pain [clinic] they come out with more medication, or injections.' [GP, female; Leeds; 319]"* (McCrorie et al. 2015). If this is the case, then whilst prescribing sits predominantly in primary care (Auditor General for Wales 2018), it would seem influences on prescribing could be greater than simply prescriber preference or lack of alternative.

It is difficult to trace the source of analgesic medication using the data sources currently available in Wales. Whilst it may appear that an opioid was initiated by the GP, it could be on the recommendation of a practitioner from another sector. Tracing the relationship between prescription and request would require

extracting out-patient communication data and the initiation of a prescription within a designated period afterwards, for example.

8.3.2 Does 'ability to pay' affect prescribing?

A major finding of this study was that opioid prescribing of all types is disproportionately higher in areas of higher deprivation. Some reasons for this observation have been previously discussed in Section 4.6. This may not be the case everywhere, however. A study from Germany, found indebtedness increased the likelihood of not receiving or taking pain medicines (Warth et al. 2019). Germany operates insurance or co-payment-based health services with potential that the observed reduction in medication use is linked to the inability to pay (Turunen & Hiilamo 2014; Warth et al. 2019). Prescription charges were abolished in Wales in 2007 (National Assembly Government 2010). However, from the data observed in this study, it is clear that prescribing was already higher in more deprived areas, prior to the elimination of Welsh prescribing charges (Figure 4.2). It was estimated that at least 50% of the Welsh population were entitled to free prescriptions prior to removing charges, equating to 88% of items dispensed (National Assembly Government 2010).

The implications of the findings of this research are that removing prescribing charges was not associated with the rise in opioid prescribing noted. However, whether lack of payment encourages prescribing is a matter of dispute (Groves et al. 2010; National Assembly Government 2010; Carlisle 2017). In Wales, annual increases in prescribing slowed following the removal of prescribing charges. Pharmacy leaders in Wales deny that prescribers are encouraged by free prescriptions for their patients. Instead, they insist that higher levels of prescribing reflect the greater prevalence of poor health in the country (Carlisle 2017).

8.3.3 Why might the legislation not have 'worked' in the UK?

Although the results shared here (Chapter 6) imply the introduction of opioid focused NPIs may have contributed to a degree of reduction in opioid

prescribing, legislation appeared to have less effect. Examining the literature raises the consideration that changes in practice may depend on the type of legislation introduced.

At the time, the murders committed by the GP Harold Shipman (Section 1.11), shook the healthcare fraternity. There was discussion of how healthcare would change as a consequence, including rebuilding trust between practitioners and patients and how competency in practice would be reviewed (Baker 2004). The TSA reported (Chapter 6) and the notable upward trends across the UK (Zin et al. 2014; Ruscitto et al. 2015; Davies et al. 2018; Curtis et al. 2019), however, implies that the impact of Shipman's behaviour and the subsequent legal changes did not impact prescribing directly. A possible explanation for this might be the area of practise that Shipman was found to have abused (Smith 2005). Most victims in the Shipman case were elderly people, some deemed to be receiving palliative care. The vast majority of opioid prescribing in Wales and the rest of the UK (Zin et al. 2014; Todd et al. 2018; Torrance et al. 2018 Curtis et al. 2019) however, was and remains, for non-cancer related pain (Section 3.5.1). Interestingly, the rates of opioid prescribing for people with a recorded diagnosis of cancer reduced in Wales between 2005 and 2015 (Appendix J).

Gomes and colleagues (2014) were able to demonstrate a combination of legislation strengthening requirements for patient identification and introducing a prescription monitoring (PMS) programme led to the number of opioid prescriptions reducing (Gomes et al. 2014). Whilst the Canadian changes were like the Shipman law changes, they appear to have been effective. In the UK, the focus of the benefits of the changes have concentrated on end-of-life care (Baker 2004; Pocock et al. 2018) and deterring rogue practitioners. In the early 2000's, when the main legal changes occurred, opioid prescribing was relatively modest and, particularly for chronic pain, prescribers worldwide were being encouraged to prescribe more (Kotecha and Sites 2013; Shapiro 2015; McGreal 2018). By the time Canada introduced PMS and legal enforcement, the opioid crisis was acknowledged in North America (Gomes et al. 2011; Franklin et al. 2012; Gomes

et al. 2014). Also, evidence of potential limitations of opioids in non-cancer pain were becoming better known (Ballantyne and Shin 2008; Campbell et al. 2015; Els et al. 2017). In these situations, perhaps the legal requirements and accompanying guidance make sense in the clinical context the prescribers are working in. This could lead to improved compliance and so the desired outcome of reducing prescribing or improving monitoring.

In Wales, changes that could be connected to the NPIs began from around 2012 and were predominantly associated with a reduction in tramadol prescribing (Chapter 6). An indicator was introduced in the 2013-14 financial year, in combination with an education pack and practice audit. This was in response to a doubling of tramadol-associated deaths over five years (from 83 in 2008 to 175 in 2012) in England and Wales (Hawkes 2013, Office for National Statistics 2019). Drug associated deaths disproportionately affect Wales compared to England and in 2012, the difference amounted to 20 deaths per million (45.8 deaths per million in Wales compared to 25.4 in England) (Office for National Statistics 2013).

As illustrated in the TOPAS data (Chapter 5), tramadol was the second most prescribed opioid in Wales between 2005 and 2015. However, it was reported to be the most prescribed opioid in a number of regions of England between 2010 and 2014 when examined by oral morphine equivalence (Mordecai et al. 2018). Anxiety in regard of the leap upwards in tramadol associated deaths led to re-categorisation of tramadol as a schedule 3 controlled drug in 2014, garnering attention from healthcare and mainstream media. Subsequent reductions in tramadol prescriptions issued in England were noted (Chen et al. 2019), corresponding with the reduction in prescription numbers noted in this study (Chapter 5).

8.3.4 Are current methods of monitoring prescribing fit for purpose?

OMEQ is a useful measure of opioid utilisation in the general population and an individual basis (Nielsen et al. 2017). This study has demonstrated differences

between assumed burden of opioid prescribing using $OMEQ_e$ and prescriptions issued, which may have important clinical implications. Evaluating opioid prescribing using OMEQ would provide easily comparable data that better reflects clinical practice.

It is important, however, to draw the distinction between using OMEQ as a means of familiarising prescribers with the concept of opioid burden, and assuming it guarantees equianalgesia in all people (Schatman et al. 2016). Whilst guidelines have adopted OMEQ as a way of setting a dose limit (Harrison and Cormack 2018) it should not be seen as something to aim for. As with any other drug, many factors affect an individual's response to opioids (Robert 2006; Trescot et al. 2008; Rennick et al. 2016; Arul and John 2020). Consequently, OMEQ, whilst a useful clinical guide, should probably not be used to assume levels of risk in an individual without also taking account of patient-specific factors such as renal and liver function, polypharmacy, age, comorbidities and so on. It is worth bearing in mind that opioid overdoses can occur at any dose, as can any adverse effects (Schatman et al. 2016). In simple terms, there is no such thing as a 'safe' dose of opioid, only the right dose for the right person at the right time for the right reasons.

The available literature on prescribing persistence indicates that duration is just as important as dose, in terms of increasing risk of harm from opioid analgesics (Cohen et al. 2008; Jain et al. 2018; Salas et al. 2020). Whilst symptoms of dependence have been demonstrated in people receiving 24 to 48 hours of opioids in acute settings (Shah et al. 2017; Liberman et al. 2019), other serious problems such as depression are associated with longer durations of use (Scherrer et al. 2016; Salas et al. 2020). Consequently, in the same vein as OMEQ, there may be no safe duration of use that suits all people. Much clearer guidance about the risks of treatment be it dose or duration, is required for both prescribers and people prescribed opioids. As Scottish prescribing guidelines have clearly explained, regular monitoring and review of people being prescribed opioids is essential (Harrison and Cormack 2018). Those reviews should not

simply focus on relief of pain, but also be used as an opportunity to appraise the balance of benefit and risk for everyone. It would seem prudent to suggest continuing opioids without evidence of benefit to the patient is only likely to cause harm (Harrison and Cormack 2018; Taylor et al. 2019)

8.3.4.1 Is there benefit to using OMEQ to monitor opioid prescribing burden?

TOPAS results imply that the way prescribing data is currently examined does not provide sufficient insight into opioid burden in communities. Although this study used an estimated measurement due to the lack of prescribing information, it does hint that using oral morphine equivalence is more reflective of what is going on in practice than simply prescription numbers or DDDs. When OMEQ was used to compare prescribing in four Nordic countries, it demonstrated noteworthy differences in patterns of opioid consumption compared to those seen with DDDs (Svendsen et al. 2011). 'Weak' opioids such as codeine, carry higher DDD values than 'strong' opioids like morphine. Countries where codeine predominated appeared to have high overall opioid prescribing, which was reversed when OMEQ was used and the contribution of 'strong' opioids accounted for (Svendsen et al. 2011). Codeine, which is commonly prescribed but often not regarded as a 'problem', contributes significantly to opioid burden in Wales. The failure to acknowledge the dominance of codeine prescribing in all its forms until recently (All Wales Medicines Strategy Group 2019) has possibly resulted in an underestimate of the potential harm being caused. Prescribers' understanding of OMEQ is poor (Rennick et al. 2016). This is particularly pertinent to products with less familiar doses. Fentanyl and buprenorphine are dosed in micrograms rather than milligrams as for most other analgesics for example (BNF: British National Formulary - NICE. 2021). The study results showed a disproportionate burden by $OMEQ_e$ compared to the number of prescriptions issued for both. Use of OMEQ as a measure of prescribing might improve comprehension of opioid equivalence and lead to safer prescribing.

Whilst overall it seems the tide is turning and opioid prescribing is starting to fall in Wales, the UK and further afield (DataLab 2017; Centers for Disease Control

and Prevention 2021; All Wales Therapeutics and Toxicology Centre 2021) attention needs to turn to 'what' and 'for how long' rather than 'how much' is being prescribed. North American data is sometimes presented as numbers of units or tablets (McGreal 2018). Whilst often very large numbers, it is not in itself an explanation of the burden as it provides little explanation of dose or duration of use. Data for OMEQ gives a much more relatable explanation of the changes in burden. Further, there is evidence from several developed countries that people are remaining on opioid prescriptions for longer periods of time (Bedson et al. 2016; Shah et al. 2017; Jani et al. 2020; Black-Tiong et al. 2021). In the UK, 18.7% of people started on >200mg OMEQ doses, were observed to remain on that level of intake for at least 2 years (Jani et al. 2020). The incidence of long-term opioid prescribing, defined by receipt of three or more prescriptions within 90 days with no more than 6 months between episodes, increased from 5.5% in 2012 to 9.1% in 2018 in an Australian population (Black-Tiong et al. 2021). Perhaps to assess whether meaningful change is being made, in addressing the concerns about opioid use and long-term harms, a measure that takes account of dose (OMEQ) and duration is needed. The ideal use of opioids appears to be lower doses for shorter periods of time (Faculty of Pain Medicine 2021).

8.3.5 Are the trends in resource utilisation and costs a sign of equality in healthcare?

In conjunction with the first phase prescribing trend results (Section 3.5 and Section 5.5), perhaps the most concerning finding from the TOPAS study are the significant disparities between areas of high and low deprivation. Higher levels of prescribing and healthcare utilisation are observed in the most socio-economically deprived areas of Wales, with high levels of poor general health and well-being (Section 4.5 and Section 7.8).

The high levels of opioid prescribing in the most deprived areas of Wales, might be interpreted by some as a perverse sign of equality. We are 'lucky' that receipt of medicines is not always related to the ability to pay in the UK (Section 8.3.2). In many parts of the world, opioids are not available, even for end of life care

(Richards et al. 2020). In Wales, in theory, anyone with access to a GP can access an opioid prescription. Is that necessarily a good thing, however?

The concerns about opioid use have already been discussed (Section 1.7), as have those about the susceptibility of people living in the most deprived areas being exposed to higher OMEQ and longer prescribing persistence than in more socioeconomically well-off areas (Section 5.6). Phase 2 results reveal that the burden placed upon health services may, in part, be associated with the use of opioids. It is far from clear that opioids benefit many people who take them (Els et al. 2017; Taylor et al. 2019). May these results perhaps point towards people developing new or worsening health problems because of their use? If so, those problems appear likely to be felt more keenly in the most deprived areas of Wales, where services are more limited or less accessible to those who would most benefit.

8.3.6 Will guidelines change prescribing in the future?

In Chapter 6, the influence of NPIs on opioid prescribing was examined. At the time of writing, Wales does not have national guidelines for either opioid prescribing or the management of pain more widely. Since the end of the TOPAS study period NICE, who are regarded as an influential source of guidance in England and Wales, have increasingly recommended against the use of opioids for some common, long-term, painful conditions including low back pain (National Institute for Health and Care Excellence 2016), neuropathic pain (Centre for Clinical Practice at NICE 2013) and recently chronic primary pain (National Institute for Health and Care Excellence 2021). NICE validate recommendations against opioids on the basis of a lack of evidence suggesting benefit and significant evidence of harm (National Institute for Health and Care Excellence 2016; National Institute for Health and Care Excellence 2021). ITSA demonstrated some reduction in prescribing associated with an opioid focused NPI, but this does not demonstrate or provide assurance that opioid analgesics are being used appropriately.

In Scotland, introducing national prescribing guidelines for pain (SIGN 136) in 2013 has subsequently been associated with an 18.8% reduction in opioid prescribing over the following six years (Hebert et al. 2021). An update to their 2013 chronic pain guidelines in 2019, reflected the changes in advice around opioid analgesics. Unlike NICE, the Scottish Intercollegiate Guideline Network (SIGN) continue to include opioids as a short- to medium-term treatment option, albeit with caveats about assessing for suitability and ensuring outcomes are regularly monitored. Where evidence of poor effect or harm is noted, dose reduction and, if necessary, cessation is supported (Harrison and Cormack 2018; Scottish Intercollegiate Guideline Network SIGN 2019). SIGN suggest doses above 50mg OMEQ need to be reviewed at least annually and for specialist pain advice to be sought when people are prescribed >90mg OMEQ per day (Scottish Intercollegiate Guideline Network 2019). Wales has no similar guidance, although practitioners working in Wales are supposed to follow NICE guidance, which should also be incorporated into Welsh guidelines where available (Welsh Government 2021). Clinical guidelines are developed within Health Boards, but the degree to which they are evidence based potentially depends on the scrutiny they are given under local arrangements. It is highly unlikely that processes as thorough as SIGN or NICE are used in those cases, resulting in variability in practise across the country.

Both NICE and SIGN have protocols for developing their guidance. SIGN consider a wider range of literature than is permitted by NICE strategies. In practise, this can result in differences in guidance issued. Opioids are an example of this, where SIGN continue to suggest they can be used albeit with caveats around monitoring and review (Scottish Intercollegiate Guideline Network 2019), whereas new NICE guidance for back pain and chronic primary pain have specifically recommended that opioid analgesics should not be offered (National Institute for Health and Care Excellence 2016; National Institute for Health and Care Excellence 2021). If the methodologies used are not well understood or explained, it can lead to misunderstanding and concerns about the implications of following the advice without context (Faculty of Pain Medicine 2021; Smith et

al. 2021). It seems each time new guidance is issued, concerns are raised that people already prescribed opioid analgesics for long-term pain conditions, who benefit in terms of pain reduction and improved function, will have them stopped (Faculty of Pain Medicine 2021) despite there being no statements to encourage that. Organisational or individual's interpretation and implementation of guidance is out of the control of the publishers, however.

NHS England have published a directed enhanced service (DES) for structured medication reviews (SMR) to target people prescribed drugs associated with dependence and withdrawal as per the PHE review (2019) (Taylor et al. 2019; NHS England Primary Care Group 2021). This should be an opportunity to enhance care and safety for, people living with pain. However, in some organisations, it could be seen as a green light for undertaking reductions of medicines even when people believe they are benefiting from taking them. If anything is to be learned from the experience of North America, in terms of their handling of the opioid crisis, it must be that stringently applying rules or restrictions on prescribers and patients alike, is unlikely to be helpful as a lone strategy to address concerns about high levels of prescribing (Schatman and Shapiro 2019; Singer et al. 2019; Sacks et al. 2021).

All influences associated with opioid prescribing need to be addressed if meaningful change in prescribing is to be achieved in time. This study has shown that, in Wales, the main factors associated with receiving an opioid prescription and in using higher levels of healthcare are being socioeconomically deprived, being female, and receiving prescriptions for more than 6 months. However, it is unlikely that guidance would be able to direct prescribers to not prescribe for people based on their socioeconomic status or gender. It is possible to highlight where risks are greatest, however, and to encourage greater scrutiny of prescribing and provide support to reduce it in areas where prescribing is highest. Clearly, of greater importance is to address the factors underlying those differences. Improving the availability of women's health services and addressing socioeconomic deprivation for example, are vital, but likely to take a long time

for change to occur. In the meantime, changing the duration of prescribing or the advice issued to people living with pain are changes that can be more easily legislated and would bring more rapid benefit to the population.

8.4 Policy direction for pain management and analgesic stewardship in Wales

If opioid prescribing is, as suggested, a surrogate for adequate pain management support (Finestone et al. 2016) and if pain experience is influenced by things other than physical pathology (Engel 1977; Gatchel et al. 2007; Stilwell and Harman 2019), it is likely that more than prescribing guidelines are needed for change to occur. Attempts have been made to address the growing health burden of pain in Wales. In 2008, the Welsh Assembly Government published service development and commissioning directives aimed at improving pain management services across the country (Welsh Assembly Government 2008). The major aim at that time was to change service delivery to improve integration, ensuring people received appropriate, evidence-based support where and when it was needed (Welsh Assembly Government 2008). In particular, the directive acknowledged the complexity of chronic pain and the need to reduce the risks of its development by improving overall health and wellbeing of the population (Welsh Assembly Government 2008).

The National Pain Audit for England and Wales (2012) had limited response from Welsh pain services beyond the first phase, which examined the composition and allocation of services (Price et al. 2012). Based on self-report, 60% (n=9) of services in Wales met the criteria for being multi-disciplinary (presence of a psychologist, a physiotherapist and a physician). The audit reported 90% of Welsh services had a consultant to undertake medication management and 30% had access to a pharmacist (Price et al. 2012). The audit did not examine how many services took responsibility for prescribing either by issuing prescriptions directly or providing follow-up support to monitor outcomes. The likelihood is that Welsh pain services make prescribing recommendations with the expectation they will be fulfilled by primary care colleagues.

It is hard to determine how the 2008 directive had influenced the provision of service only 2 years later and no validated data on service provision in Wales, appears to have been collated since. The research presented in this thesis suggests, however, that regardless of specialist service provision, the use of opioid analgesics significantly increased after the 2008 directive. If opioid prescribing is inversely associated with pain management support (Finestone et al. 2016), the implication of the data is either that investment in secondary care services had minimal impact in primary care or the prevalence of pain was out-running any expansion in support over the duration of the study.

In 2019, WG launched new guidance, '*Living with persistent pain in Wales'* (Welsh Government 2019). The basis of the new guidance to Health Boards, professionals and people living with pain was new approaches to healthcare in Wales (Welsh Government 2019). Reducing the burden of long-term conditions in Wales by improving integration of health and social care whilst also addressing issues such as educational and housing disparities are at the heart of recent WG public health policies (Atherton and Welsh Government 2019; Welsh Government 2019). Currently, however, pain as a long-term condition does not have the same level of political interest as other long-term conditions, despite the concerns expressed about the consequences of failing to improve its management (Welsh Government 2019).

Trying to reduce opioid prescribing without addressing the reasons why people experience pain, why they feel unable to manage it or how physical and emotional conditions predispose people to it, seems to some extent a futile exercise. Significant investment will be required to reduce the current inequalities seen in areas of significant deprivation (Section 1.10), including providing employment opportunities, increasing social cohesion and normalising pain as something that does not always need medical intervention.

8.4.1 Drug monitoring and prescribing databases

It is important to improve life opportunities and reduce socioeconomic disparity in order to reduce the pain prevalence over an extended duration. However, the risks of continuing opioid prescribing at the current levels noted in Wales (All Wales Therapeutics and Toxicology Centre 2021, Welsh Government and Stats Wales 2021) and described here, are a significant burden on public health and wellbeing in themselves. Despite there being multiple sources of data on medicines and prescribing here in the UK, it is not clear they are being used optimally to impact policy and practise in a timely manner or to pre-empt changes in variables, which could signify a concern. Examining the sources of information used in the UK and how prescribing data are used elsewhere is helpful to highlight where systems here could be improved for the benefit of the wider population.

The UK has the Yellow Card scheme to report adverse events related to medicines and medical devices (Medicines and Healthcare products Regulatory Agency 2021). Overseen by the Medicines and Healthcare products Regulatory Agency (MHRA), professional or patient-reported incidents are collected, and warnings issued when patterns of concern are noted (Medicines and Healthcare products Regulatory Agency 2021). Whilst overdose might be deemed by some as an adverse effect of medication, incidence data for England and Wales is not collected by MHRA but the Office for National Statistics (ONS) (Office for National Statistics 2019). Data on people accessing services for substance misuse are collated and analysed separately in Wales, Scotland and England (NWIS - Information Services 2019, NHS Digital 2021; Public Health Scotland 2021).

In terms of prescription data, the largest source in the UK is in England, where the majority of the UK population reside (Office for National Statistics 2021). Since 2015, the OpenPrescribing project has provided an interface to search English prescribing data to practice level, some of it dating back to 1998. It claims to be capable of interrogating drug data to dose level, although on closer inspection, this refers to product dose rather than the dose prescribed per

individual (Curtis & Goldacre 2018). Whilst allowing easy trend analysis, OpenPrescribing is not a linked dataset and examining trends within different demographics still requires data from other sources. An example of this would be the paper produced by Curtis and colleagues (2019) examining opioid prescribing trends where socio-economic deprivation status was based on location of the prescriber rather than recipient, with freely available data taken from Public Health England. Further, age-based analysis was based on published proportions of registered patients in each practice (Curtis et al. 2019). So, whilst providing a comprehensive way of looking at prescribing trends, OpenPrescribing still lacks detail that would be helpful to provide insight of correlation (OpenPrescribing 2020).

Wales operates a reasonably similar system, allowing scrutiny of prescriber level prescribing data, but only as far as drug formulation and strength (Welsh Government and StatsWales 2021). More detail is available for registered NHS employees, from the Shared Services Partnership by downloading individual scanned prescriptions, where some demographic data can be sought. Also, dose, form and quantity of each prescribed medicine can be taken from the scanned prescription, although it is not a realistic means of research as prescriptions can only be viewed one at a time (Shared Services Partnership 2021). Similarly to English data (OpenPrescribing 2020), there is a lag in data release due to prescriptions needing to be physically received and remunerated before the data is confirmed (Shared Services Partnership 2021).

In Scotland, prescribing data are securely stored by the Information Services Division (ISD) of NHS National Services Scotland (Public Health Scotland 2021). This allows analysis to individual patient level of all prescriptions issued, including the date, dose, formulation, strength and quantity of all medicines dispensed (Torrance et al. 2018). A unique identifier, assigned to each person whose data is stored (Community Health Index number (CHI), provides demographic data including gender and postcode and is also used by other datasets, allowing linkage (Torrance et al. 2018; Public Health Scotland 2021).

The Information Services Division appears to operate the most complete prescribing review system in Great Britain at the moment and also has a shorter time to publishing than the English or Welsh data , although it still remains a retrospective system (Public Health Scotland 2021).

Unlike the UK, in America, Canada and Australia, national real-time prescribing monitoring is in place. Large datasets are created and added to, which are used to examine prescribing trends (Sproule 2015; Department of Health, Australian Government 2019; Centers for Disease Control and Prevention 2021). The idea was for opioid prescribing monitoring to capture incidents of doctor shopping and duplication prescriptions, which may point towards misuse (Ayres & Jalal 2018). Sharing data within and between states was seen as a method of tracking the crisis, including whether the demographics of people affected changed. In theory, this would provide opportunities for targeted interventions (Martinez 2018; Ayres & Jalal 2018). It is mandated in the majority of States, prescribers must check the prescription monitoring database before issuing certain controlled drug prescriptions. Public health officials and law enforcement are also encouraged to access the data to identify rogue prescribers and dispensers, targeting so-called 'pill mills' which have been associated with high levels of misuse and deaths in some communities (Chang et al. 2016; Butler et al. 2018; McGreal 2018). The Canadian Province of British Columbia introduced real-time monitoring (PharmaNet), which linked pharmacies and hospitals to a central database in 1995 (Wilsey et al. 2009; Dormuth et al. 2012; Wilsey & Prasad 2012). A similar system was launched in Australia in 2019, with both systems providing real-time prescription monitoring producing alerts to regulators and healthcare professionals to patients who may be at risk of harm or could be misusing prescribed opioids (Department of Health, Australian Government 2019). Effectiveness of prescription monitoring has been reviewed and shown to be associated with reductions prescribing (Dormuth et al. 2012; Chang et al. 2016; Lachance & Frey 2019; Wilson et al. 2019; Dobbin & Liew 2020; Fetene et al. 2020). Initially following the introduction of monitoring programmes, large reductions in prescribing were noted. For example, British Columbia observed a

32.8% reduction in inappropriate opioid prescriptions (where inappropriate was defined as a prescription within 7 days of a prescription for 30 tablets or more) within six months of PharmaNet implementation (Dormuth et al. 2012). The reduction was sustained over the subsequent two years, with a further small reduction towards the end of the second year. A similar reduction and sustained lower level of prescribing was noted for benzodiazepines within the same system. The authors do not provide information about the impact on individuals' pain management experience or healthcare services (Dormuth et al. 2012).

In Florida in the late 2000's, 4% of registered prescribers were responsible for 67% of opioid volume, equivalent to 40% of prescriptions dispensed. The percentages were unchanged following the introduction of prescribing monitoring in 2010, although reductions in overall patient and prescription numbers were observed. The system did not lead to people highlighted as high-risk prescribers (high volume, high dose, high patient numbers) becoming lower risk however (Chang et al. 2016). These examples imply prescription monitoring systems may contribute to a reduction in high-risk prescribing. A systematic review from 2019, using predominantly North American data, examined the effectiveness of prescribing monitoring systems to change opioid prescribing volume, use of multiple providers, inappropriate prescribing and non-medical opioid use (Wilson et al. 2019). Whilst some studies were able to demonstrate a reduction in opioid prescribing, overall, the outcomes appeared inconsistent. Whilst some states with prescribing monitoring reported significant reductions in prescribing, others were unable to demonstrate any changes. Similarly disparate outcomes were noted for different schedules of opioids, although 2 of 3 studies reported decreases for schedule II opioids such as oxycodone and hydromorphone (Wilson et al. 2019), which have been most closely associated with misuse and overdose related deaths in the USA (McGreal 2018). Both studies included in the review which examined the incidence of inappropriate prescribing, demonstrated a reduction. A decrease in nonmedical prescription opioid use, which has been associated with many of the deaths in North America (McGreal 2018) was not noted in either included study (Wilson et al. 2019).

Further, none of this work has examined the personal impact on people living with pain.

Of course, not all opioid prescribing is considered high-risk, either by the prescriber, the patient or perhaps even by society. As the Florida study highlighted, a small minority of prescribers are likely responsible for the majority of the 'worst' practice (Chang et al. 2016). Consequently, protections are needed for monitoring systems, to ensure legitimate use of opioids is not affected or negative repercussions are inflicted upon prescribers or patients if data is misinterpreted or not analysed in context.

Whilst an abundance of prescribing and dispensing data is available in the UK (Curtis and Goldacre 2018; All Wales Therapeutics and Toxicology Centre 2021; Public Health Scotland 2021), it is not currently used as a monitoring system for active prescriptions as seen elsewhere. It has been suggested the UK adopts prospective prescribing monitoring system (Stewart & Basler 2013). Given the experience of other nations, such a system could be initially useful at least. Long-term outcomes of prescribing monitoring schemes are less clear but there is perhaps, an argument to be had that some record of who is receiving potentially harmful medicines is better than nothing.

TOPAS has demonstrated the value of examining prescribing patterns in demographic groups and how it may allow more targeted interventions to reduce harm. This would be even more valuable if the data were available rapidly after collection. A deep learning model to classify patients receiving opioid analgesics and stratify their risk of developing misuse was designed and shown to be robust by a group in America (Che et al. 2017). The researchers were able to link prescriptions to diagnostic records in order to determine criteria for short and long-term prescribing, opioid-related adverse events and use them to predict the likelihood of future outcomes such as long-term opioid use (Che et al. 2017). How realistic such a complex system could be used in clinical practice and

what advantages it confers over established prescription monitoring systems is unclear, however and warrants further research.

It is likely more cost-effective to prevent disease than treat it when it occurs. However, it is common that greater investment is made to treat illnesses within a healthcare system than taking a more societal view and looking at the role of non-medical interventions (Lyons et al. 2014). It is especially pertinent when deprivation is a key driver of poor health and poor health outcomes will not be solved by medical treatment alone (Marmot & Bell 2012; Marmot 2017). Joining seemingly disparate data from different public services (e.g., healthcare, and social services) at an individual level should allow greater insight into how services interact, and people interact with them. Combining information may enable relationships to be identified between factors that would not be evident from a single source (Green et al. 2015). It is perhaps one of the greatest potentials of big data. In the UK, public services are incredibly important personally and politically. Using data that is being collected routinely seems logical, to determine outcomes, value for money and to inform plans for future development.

8.4.2 Learning from our Celtic cousins

Wales has much in common with Scotland, in respect to population levels of poor health, historically high levels of socioeconomic deprivation (Bambra 2016) and a high incidence of drug misuse relative to the general population (Liddell 2019; Scottish Affairs Select Committee 2019). Like Wales, concerns about opioid prescribing in Scotland have been expressed but, unlike Wales, research groups have been investigating pain and analgesic prescribing for some years already (Torrance et al. 2014; Ruscitto et al. 2015; Torrance et al. 2018; Torrance et al. 2020). Policy development to address chronic pain and prescribing is underway in Wales (Francis 2021) and it seems sensible and prudent to take lessons from the work already undertaken in Scotland, to assist that process.

Work to improve the way pain was managed and, consequently, address associated issues including rising opioid prescribing started in Scotland in 1994 with a Scottish Office review of the support available to people with chronic pain (NHS Quality Improvement Scotland 2007). It suggested there was a good base on which to build. Further reviews in 2002 and then by McEwen in 2004 observed that whilst chronic pain services were accessible to people all over Scotland, they were not physically present in all areas (McEwen 2004). Due to the way services had developed, often down to the goodwill and tenacity of local professionals, it had led to piecemeal provision, not always supported by adequate funding and facilities (McEwen 2004). McEwen observed mounting waiting times compared to the data from the early 1990s although this was likely a reflection of increasing demand for support. Sixteen recommendations were made to every health board to develop either integrated acute and chronic pain services or a lone chronic pain service. This included an urgent review of pain service provision, ensuring it was adequate for the population, had an identified budget and could provide accurate and timely data. There was also a recommendation for health boards to communicate effectively between sectors, in regard of the services available and improve seamless care. Furthermore, formal links with community services and vocational rehabilitation support were to be established in each service (McEwen 2004). Of real importance in the McEwen review were recommendations on the need to take a national approach to improve quality and collaboration, in part to develop comparative data. Emphasis was given to properly evaluating new developments, effectively disseminating good practice, and building a culture of research. Finally, adding to the national approach, agreeing on a system which provided timely access to routine data from chronic pain services and a co-ordinated national education and training programme was encouraged (McEwen 2004).

Like Scotland, the 2008 directive in Wales acknowledged the complexity of pain, acute and chronic, and the need for widespread change to improve access to services. As with the McEwen recommendations, key actions included an assessment of local needs and developing local pathways to improve access in

primary and secondary care. Also, regular periodic monitoring of medicines for chronic pain and development of guidance and support on prescribing (Welsh Assembly Government 2008). What the Welsh directive lacked however, was the academic monitoring incorporated in Scotland. Whilst laudable, the actions suggested in Wales did not include detail of how they might be reviewed, relying on health boards, the Welsh Pain Society (a small membership group which is not an official chapter of the British Pain Society), local authorities and Welsh Government to self-monitor. Research in respect of examining the burden of pain in Wales or the impact of introducing new services, trends in prescribing and so on, were not included at all. In researching this thesis, no data was available from Welsh Government on current levels of service provision or whether or how issues around pain and its management had been included in research programmes or funding streams in the intervening years (Francis 2021). Given the burden on health services, as demonstrated in this thesis, the social and wider economic implications of pain, lack of Wales-specific research and formal service review could be a problem. Without baseline data, how will improvement be measured and how will service users and providers know when 'good' is achieved?

In contrast, Scotland has undertaken successive reviews of pain services since 1994, assisting in maintaining focus on pain as an important health and social issue. Getting relevant information on Pain Services (GRIPS) became a highly influential benchmarking exercise in Scotland (NHS Quality Improvement Scotland 2007). An important outcome from the review was that, in Scotland, chronic pain became recognised as a condition in its own right and a national lead clinician for chronic pain appointed (Gilbert et al. 2014). Whilst this could appear simply a paper exercise, Scotland's experience demonstrates that, by drawing focus and providing strong clinical and political leadership, progress can be made.

A national steering group was created for Scotland in 2009 and developed a service model for chronic pain, recognising the majority of people receive pain

management care and support in primary care rather than specialist centres (Breivik et al. 2012; Gilbert et al. 2014). Similar recognition of increasing support to primary care, was given in both 2008 and 2019 Welsh guidance on pain service development. Admitting the difficulty access support for pain management and the shortcomings of practitioners knowledge and importantly, time needed to undertake complex case work in primary care is vital. Not least, as most prescribing takes place in that sector and tends to be main intervention that can be easily made when someone presents with pain (McCrorie et al. 2015; Mills et al. 2016; Gordon et al. 2017).

As already discussed, (Section 8.3.6), national prescribing guidelines were introduced in Scotland in 2013 (Scottish Intercollegiate Guideline Network SIGN 2019) and were used as a means of educating practitioners and raising awareness of pain. This was accompanied by the launch of a dedicated website providing quality assured information accessible to people living with pain as well as those supporting them (Gilbert et al. 2014). Some information is available from national websites in Wales (All Wales Medicines Strategy Group and All Wales Therapeutics and Toxicology Centre 2020). However, developing a single site with nationally agreed resources, would help practitioners and patients alike, as there is a huge amount of information available on the internet, which can be difficult to navigate or be confident is up to date and clinically accurate.

Despite all the work which has been undertaken in Scotland to drive improvements in allocation of pain services, reduce disparity between different geographical areas and develop a national approach to pain management, more recent reviews still found areas requiring attention. Some variation in care continued in 2018. Data from Health Boards on service provision (Mellor and Chronic Pain Project Group 2018), despite core data measures being agreed (NHS Quality Improvement Scotland 2007) remained difficult to obtain.

Scottish quality prescribing guidelines for chronic pain were launched in 2018, again, including data measures to provide comparison across the country

(Harrison and Cormack 2018). Like having national clinical leads to drive improvement forward and keep pain on the political agenda, the quality prescribing guidance is promoted in each health board by clinical staff, one of whom tends to be a pharmacist but without needing to be a pain specialist per se (Harrison 2018). As pain is ubiquitous to all sectors and specialities, wide promotion of good practice in prescribing is likely to become a meaningful intervention. The guidance gave a three year timescale to implement change, which does not preclude annual reviews but, gives a more realistic duration over which alterations in practice are likely to take place (Harrison and Cormack 2018).

In Wales, no currently agreed measures or standards exist for health boards to benchmark services. As discussed, (Section 6.6.5), national prescribing indicators may have had some effect on the number of opioid prescriptions being issued in Wales but does not appear to have impacted the overall burden of opioids (Section 5.5). Introducing quality prescribing guidelines, adapted from the Scottish document, has recently been agreed by the All Wales Prescribing Advisory Group (AWPAG) in addition to national prescribing advice (All Wales Prescribing Advisory Group 2021). Nationally agreed guidelines for a range of clinical conditions are becoming commonplace in Wales (All Wales Therapeutics and Toxicology Centre 2021). There are benefits for reducing country-wide variation and gaining local agreement to implement. Differences in individual practice and opinion can drive local guidelines or practice, even if it is not in line with the evidence base for the condition (Scott-Thomas 2020).

What is clear from the experience of colleagues in Scotland is meaningful and lasting change in practise takes time and a huge amount of determined and co-ordinated work. Whilst Wales has started on the process, a massive amount of work is needed still. Scotland had developed a national strategy, benchmarked services, and determined to appoint a national clinical lead in 2008, when Wales was politically, only just recognising the need to address chronic pain. Wales is 10 years behind, in terms of developing a nationally agreed approach to

supporting people living with pain. Whilst some progress is being made in terms of reducing opioid prescribing (Welsh Government and Statistics for Wales 2020; All Wales Medicines Strategy Group 2021) pain education for practitioners and people with pain remains widely variable, service provision is patchy and links with third sector organisations and social care are not well developed in all services. Hence, prescribing initiatives alone will not improve pain management as a whole.

There is a pressing need to develop high quality data and research in Wales in all aspects of pain, management, and prescribing. The regular review of Health Board level services and prescribing, as seen in Scotland, seems to have contributed to maintaining motivation and attention for making improvements. Policy change without an accompanying research plan would seem to limit all parties' ability to determine what progress is made or how it affects the lives of people living with pain.

As a starting point, investigating why prescribers continue to prescribe opioid analgesics and why people with pain seek them, in preference to other management methods, within the Welsh context would be useful for shaping future policy and guidance. Data drives many healthcare developments nowadays. It is possible the SAIL databank may be able to extract relevant data to provide some sort of baseline measure of pain prevalence in Wales. Details of services can be requested from Health Boards and compared to nationally agreed standards set out by the Faculty of Pain Medicine (Faculty of Pain Medicine 2021) as used by the National Pain Audit (Price et al. 2012).

Measures to effectively monitor opioid prescribing will need some thought. As presented in this thesis (Section 1.11.1), what constitutes high population levels of prescribing is not necessarily agreed. Whilst an agreed maximum oral morphine equivalent dose might be accepted, (Faculty of Pain Medicine 2021) it is difficult to determine who is most at risk from the data currently available. It would be prudent to determine a national measure of opioid risk, that could be

used to highlight individuals or areas most at need of intervention. Incentive schemes or funding opportunities need to be directed more towards people and communities who face the highest risk if opioid analgesics are continued. This thesis provides evidence of factors which could guide data identification including gender, age, duration of prescribing and socioeconomic deprivation.

8.5 Strengths of this research

This thesis contains the first large scale examination of opioid prescribing using linked healthcare data in Wales. It provides a new perspective on the trends noted from other sources (Welsh Government and Statistics for Wales 2020), which focus on numbers of prescriptions or DDDs (Section 8.3.4.1).

The results of the first part of the study (Section 2.4) presented here have examined gender (Section 3.5.3), age (Section 3.5.4) and drug-type (Section 3.5.2) associations with prescribing and set a baseline for future research into opioid analgesic prescribing in Wales. The methods adopted could be used to look at prescribing trends of other analgesics and the relationships between different medicines and the people receiving them. More detailed examination of prescribing by socioeconomic deprivation (Section 4.5) points to health-divides between areas of Wales. Social determinants of health are increasingly important for setting health policy (Marmot 2017) but are currently not included in standard reporting of prescribing in Wales. Sharing the findings of this research with Welsh Government will be a crucial step in improving the quality of data used to understand prescribing trends. Knowing where there are elements of higher risk should also better direct resources to support changes in practice.

This is also the first examination of possible associations between opioid prescribing and healthcare resource utilisation in Wales (Section 7.8). The study was able to demonstrate clear differences in resource utilisation between people receiving opioid prescriptions and those who did not. Whilst the exact costs are likely to be underestimated, due to the limitations of data extraction, the differences between groups are notable (Section 7.10.1). Whilst not undertaken

for this study, the data should allow inquiry of differences in resource utilisation in different areas of Wales. It would be valuable to undertake such analysis as part of ongoing research in this area. Linked data from the SAIL databank allows the opportunity to examine a range of health and social care interactions for individuals, communities, and the wider population. The choice to use the SAIL databank for this research was deliberate and entirely due to the ability to examine data to an individual level and across a range of healthcare services. It is hoped this study demonstrates the value and normalizes the use of large, linked datasets to determine prescribing trends, ideally in real-time.

The SAIL databank allows access to a substantial proportion of the population's data, thus reducing selection bias. The results are highly likely to be genuinely reflective of the Welsh population as there are good levels of representation of people living in all Health Board areas of Wales.

8.5.1 Impact and influence of this research

Research findings have been shared with Welsh Government and NHS Wales organisations in order to inform practice and policy development, during the course of thesis development. Locality specific data has been sent to Medicines Management Units in each of the seven Health Boards, to enable them to target opioid stewardship strategies as part of work to rationalise prescribing in line with NPIs. The outputs of the study, with particular reference to socioeconomic deprivation were shared with the Chief Pharmaceutical Officer for Wales and the Lead Civil Servant for long-term health conditions, to inform policy discussions within Welsh Government.

Based on the work examining $OMEQ_e$ burden presented in this thesis, AWTTC has adopted the category of high-dose opioid prescribing for the 2022-2023 NPIs. The $OMEQ_e$ lists developed for this study have been used to guide audits of prescribing for Health Boards and shared with the software company who provide Primary Care General Practice support as part of work to develop more effective, timely monitoring of prescribing.

8.6 Limitations of the research presented

8.6.1 Limits of data extraction

The data presented in this thesis is formed from prescribing information from Primary Care in Wales, until the end of 2015. At the time of data extraction (2017 to 2019), data for 2016 onwards was incomplete and therefore, not released as part of this research. Although provision was made within the original protocol to run a subsequent extraction towards the end of the research period, circumstances did not allow it. This resulted in the data being five years out of date at the time of thesis preparation. It would have been informative to examine trends since 2015, to see how they have changed and whether more recent guidance and the increased publicity around opioid prescribing in Wales and the UK in general has had an effect.

Analysis of data stratified by Health Board and deprivation quintiles has been undertaken as part of this study (Appendix I). Geospatial analysis using LSOA level data (Schifanella et al. 2020) would provide greater insight to more precise areas of high prescribing which could then be linked to other criteria such as employment status, receipt of benefits and geographical location (e.g. urban or rural) and would allow more precisely targeted interventions from policymakers, healthcare and social support services. The study was designed to provide baseline analysis as no similar research had previously been undertaken into opioid prescribing in Wales. However, given the significant differences between deprivation quintiles which have been revealed at national and Health Board level (Appendix I), more detailed analyses are warranted.

For the prescribing persistence analyses, annual trend data were adapted from data originally extracted from the SAIL databank. Initially, the way the data were coded was unclear, reducing confidence to track concurrent prescriptions as had been planned. Extracted data were recoded as a double check, but results demonstrate a large increase in the final year of trend analysis. This is because data was counted from the end of the prescribing period backwards, rather than prospectively from the start of the period. If repeating this work or undertaking

new analysis, consideration of how best to record persistence trends is needed, to avoid skewing the data. Using a 6-month cut off, regardless how long an individual remains on the opioid, may be one such way.

As discussed, there are limitations to using time series analysis alone for the purposes of forecasting changes in the complex process of prescribing. It would have been preferable to access data beyond 2015, to determine the accuracy of predictions made using the models developed. At the time of data extraction, SAIL was only able to provide full datasets up until the end of 2015. The study protocol and IGRP with SAIL included provision for data up until 2019 but this was not possible in the event.

Figures were drawn using opioid data from NHS Wales Shared Services, comparative analysis system for prescribing audit (CASPA) data (Shared Services Partnership 2021), the national repository for medication dispensing records in Wales (Figure 8.1). The data, at the time of this study, could not be linked with other databases in the SAIL databank. Consequently, it is not possible to link to individuals to determine the number of people to whom the prescriptions were issued. As the data is not the same as used for the TOPAS study analysis, it is included to demonstrate the shape of the trend that has been noted in the country since the end of the TOPAS study in December 2015 rather than an accurate comparison with the predictions made.

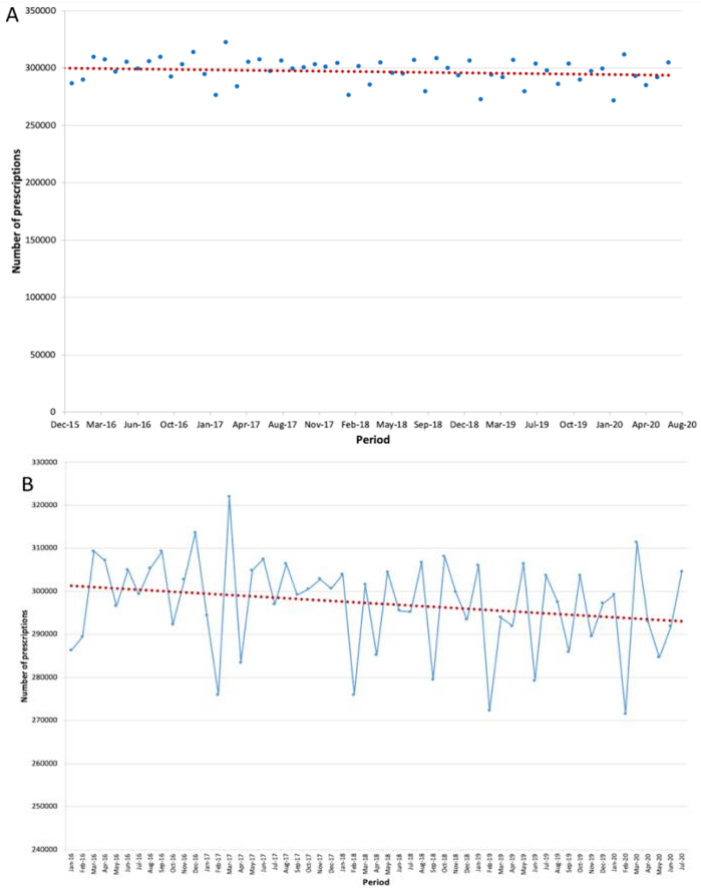


Figure 8.1: Trend of opioid prescribing in Wales from January 2016 - July 2020 using prescription dispensing data taken from CASPA . Linear trend lines added. A – Monthly number of prescriptions with linear trend line. B – Close up of monthly trends that shows similarity with seasonally adjusted data noted from TOPAS study results.
NB. Data includes all prescriptions dispensed by community pharmacies and dispensing practices in Wales and therefore, may include prescriptions issued elsewhere in the UK

8.6.2 Absence of dispensing data

Drug costs were not included in the estimations presented here. At the time of the data extraction, the SAIL databank did not have access to dispensing data or all of the detail of what was prescribed at source. This meant that it was not possible to calculate exactly what dose or what quantity of medicine each individual received. Consequently, it was not possible to calculate what was spent on medicines during the study period. Whilst national prescribing data is available, it is not possible to assign each prescription to any of the anonymised individuals whose data was examined for the TOPAS study. When dispensing data becomes available to the SAIL databank, it should be used in place of prescribing records to link to other datasets and continue to regularly analyse changes in opioid use and associated healthcare utilisation.

This study examined total opioid exposure over time. Due to research constraints, it was not possible to analyse OMEQ changes in combination with prescribing persistence as other researchers from the UK have done (Jani et al. 2020). As more evidence becomes available in regard of risks of opioid dose and duration, a Welsh perspective would be helpful and should be considered as a piece of future work.

8.6.3 Defining variables

The oral morphine equivalence and prescribing persistence measures used in this study were estimations borne of necessity due to limitations in accessible data. The results presented here are therefore likely an underestimation of both opioid burden and longevity of prescribing. As prescription dispensing data becomes available through the anonymous linkage systems of the SAIL databank, it will allow more accurate analysis of both variables by using dosing instructions and quantity prescribed to calculate OMEQ and duration (Zin et al. 2014). The data presented here was not able to accurately assess OMEQ per person or track that trend over time for example. Whilst other UK studies have looked at those variables, there is not currently, good quality Welsh data available. It is important for policymakers and clinicians to understand individual as well as population data, particularly as overall prescription numbers appear to be reducing.

For Phase 2, matching of case and control subjects used a method advocated by SAIL but was hampered by the disproportionate number of individuals with the diagnoses of interest also receiving opioid analgesic prescriptions. Further research is needed in Wales to provide more detailed analysis and controlling for non-pain comorbidities, to accurately determine the impact of prescribed opioid use on the type of healthcare accessed.

In relation to healthcare utilisation, it was not possible to retrieve the level of data necessary to make definitive statements about attendance rates. Reliance on a third party for data extraction necessitated compromise and led to less

complete data than would have been ideal. For example, this study was not able to differentiate between primary care visits in person and interactions which might have been made by telephone, might have been a prescription request or a request for an appointment. Similarly, some data was available on the specialty that individuals attended for outpatient appointments, but it was not complete. Linking of attendance in different healthcare sectors would be beneficial in furthering understanding of how people use health services.

Only a small number of possibly pain related attendances were flagged as reasons for attendance at ED. This was determined as unreliable and further analysis using all possible attendance or diagnosis codes would provide greater insight. It is likely some admissions are not recognised by clinicians at the time as associated with opioid use and therefore, would not be picked up by the coding used for data extraction. Having access to all diagnosis codes would allow investigators to make a judgment on whether presentation could have been influenced by opioid use in some way.

The admitting and discharging specialty were recorded for in-patient admissions. However, data on interventions and investigations were not provided. Determining the possible contribution of opioids to admissions for case subjects when compared to the control group was not possible. There was also no record of whether admission was planned (elective) or not (emergency), which would have cost implications. Based on unit costings used in this study (Curtis and Burns 2015; Department of Health and Social Care 2015), elective admissions were more costly than emergencies. This seems counterintuitive, as emergency admission conjures an impression of a person being more unwell and needing greater input, initially at least.

8.6.4 Absence of qualitative data

At the outset of this research study in 2015, it was hoped to include an element of qualitative research, building on the work of McCrorie et al (2015) and others in examining the thoughts of patients and practitioners receiving and prescribing

opioid analgesics. It was considered that initial data extraction would guide development of such work by revealing particular areas of interest that could then be examined through interviews and focus groups. Due to delays in the release of extracted data and its subsequent analysis, it was not possible to pursue the qualitative element of the study. It should form, however, an important element of future research, as detailed in the following section.

8.7 Ideas for future research

8.7.1 Integrating prescribing and dispensing data

This study is based on prescribing data, e.g., what a GP, pharmacist or nurse writes on a prescription in primary care. This does not always result in the prescription being dispensed and the intended patient receiving and taking the medicines as prescribed. In truth, it is not possible to examine what is taken by people who are prescribed medicines, certainly not at population level. Dispensing data is the closest estimate of what is taken but at the time this study was conducted, was not available to be anonymously linked within the SAIL databank. As that data becomes available to SAIL, it would be preferable to use linked dispensing data to examine opioid trends as it provides a more detailed picture of individual and population use.

Detail of the doses and quantities prescribed would also lead to clearer understanding of prescribing persistence and OMEQ prescribing. More timely access to prescribing and dispensing data would allow in-time and in-depth monitoring of changes in opioid prescribing, the opioid burden in the population and responses to guidelines and legislation that may be introduced in future. It would enable policy makers and clinicians to react more quickly to changes and better target resource to areas of concern.

8.7.2 Professional differences in prescribing

The SAIL databank was unable to provide data on the profession of the prescriber for this study. As part of understanding reasons for such wide discrepancies in prescribing by deprivation quintile, it would be pertinent to find

out more about the prescribers and their motivations for choosing to prescribe opioids to different patient types. Previous research to examine motivation has taken a qualitative approach (McCrorie et al. 2015; McIntosh et al. 2016) and this should be replicated amongst health care practitioners and people with lived experience of opioid analgesic use, in Wales. Better understanding of what underlies decision making, by prescribers and patients (McCrorie et al. 2015), is also helpful for developing strategy to address the issues raised and provide more targeted and appropriate interventions in different areas and amongst different populations. Wales has seen a large increase in the number of non-medical prescribers (professionals other than medical doctors) (Alghamdi et al. 2020). Representatives of all healthcare professionals who are legally able to prescribe opioids, should be included in any such research in future.

8.7.3 Socioeconomic deprivation

Pain intensity is reported to be higher in areas of greater socio-economic deprivation (Todd et al. 2018) but measures are not routinely collected in clinical practice (Stanos et al. 2016; Bertakis et al. 2004)**.** Whilst people may report having pain, it is not consistently coded in primary care. For this research, the primary care general practice database was scrutinised for codes related to known pain conditions such as osteoarthritis or back pain. The data was used to define groups for the Phase 2 study which examines resource utilisation (Section 7.4.2). However, the presence of a potentially painful condition does not necessarily correlate with presentation due to pain (Tracey 2016). A decision was made not to use diagnosis alone for the purpose of assessing changes in pain presentation over time. Further research to examine correlates between prescribing and pain reporting would need to access alternative data sources. Other studies have used data from the Health Survey for England (Todd et al. 2018) which includes questions about individual's experience of pain and analgesic use. The Welsh Health Survey does not currently include questions specific to pain intensity or analgesics (Perks and Roberts 2016).The UK Biobank has been used to collect self-reported data relating to pain experiences and

medication use (Macfarlane et al. 2020). Extracting Welsh data from the UK Biobank and linking to other existing sources using the SAIL databank linkage systems should be investigated as an option for future research.

Reasons for disparities in opioid burden between areas of deprivation need further investigation. Lack of availability and acceptability of non-pharmacological management and services have been suggested among reasons why prescribing is favoured (McCrorie et al. 2015; Finestone et al. 2016). As discussed earlier in this chapter, provision of pain management support services across Wales, with particular reference to areas of greater deprivation, is also needed.

8.7.4 Gender differences in opioid prescribing

It was clear from the results presented here that women receive significantly more prescriptions for opioid analgesics than men. However, there were signals in the data indicating men might receive higher doses than women, which warrants further examination. Reasons for differences both in pain presentation and analgesic use in men and women have been considered in this thesis (Section 1.8, Section 3.6.5 and Section 4.6.3). Further investigation into the reasons for presentation and what differences exist between genders, in that respect, would enable researchers and clinicians to better understand the quality of management currently being provided. It would also be interesting to examine associations between pain presentation, opioid prescribing and the availability of gender-specific services such as women's health or gynaecology services. This research could use linked data available through the SAIL databank, in relation to service use and prescribing. However, it is also important to capture qualitative data from women and men accessing services and how their experiences differ, as well as practitioners interacting with them.

8.7.5 Race and intersectional differences in prescribing

There is building evidence of racial bias in both access to pain management support and in analgesic prescribing (Trawalter et al. 2012; Hoffman et al. 2016;

Ghoshal et al. 2020). An editorial from the USA highlighted Latinix patients were only half as likely to receive opioid analgesia when presenting with long-bone fractures as non-Latinix white patients. Black patients were more likely to be denied opioids at all in those circumstances (Ghoshal et al. 2020). Race or ethnicity data was not available from the SAIL databank for this study although it is possible to access it. It is fair to say that Wales as a country, is not particularly ethnically diverse. People who are black, Asian or part of another minority ethnic group comprise just under 6% of the Welsh population in 2020 (StatsWales 2021). The three largest cities in south Wales (Cardiff, Swansea, and Newport) have the majority black, Asian and ethnic minority representation. Swansea and Newport are also significant areas of deprivation (StatsWales 2019). It would be valid to undertake further research examining whether racial differences existed in opioid prescribing and how it might compare with the deprivation data presented in this study and the implications for service provision.

8.7.6 Determining effects of long-term opioid prescribing

Researchers have used different criteria to determine chronic opioid prescribing. For example, ten prescriptions in a 12-month period have been used as a measure of persistence in a number of studies (Boudreau et al. 2009; All Wales Medicines Strategy Group 2015; Bedson et al. 2016; Thielke et al. 2017). Jani et al. (2020) and Black-Tiong et al. (2021) both defined long-term prescribing as being in receipt of three prescriptions within a 90-day period (Jani et al. 2020; Black-Tiong et al. 2021). Further research should assess which measures produce more clinically meaningful data, by reflecting what happens in practice. Comparing data for persistent but intermittent opioid use and persistent prescribing as defined for the TOPAS study, could also shed new light on the impact of long-term opioid use. It appears exposure duration may be more clinically significant than dose for a number of adverse effects, including depression.

8.7.7 Cost-effectiveness studies

All health care interactions take time, use resources, and have an associated cost, so it is still necessary to be aware of their impact. It can be confidently stated from TOPAS results, however, that interactions were significantly higher between people using opioids and primary care practices, regardless of the reason for them. Further research, which includes quality of life measures would provide an indication of the cost-effectiveness of opioid analgesics within a wider healthcare context and provide comparison with other methods of pain management. This would be especially interesting to examine over the mid to long-term given the persistent nature of pain for many people.

8.7.8 Examining outcomes

This study has examined prescribing and associated healthcare utilisation. What it has not been able to examine is the outcome for an individual or demographically defined group. The far higher healthcare utilisation by people receiving opioids may, in part, be due to people being seen as more unwell, hence the prescription. However, opioid-induced poor health is another possible explanation. This study examined healthcare utilisation during the period of opioid prescription. Future studies examining whether there is a change in healthcare interactions following the initiation of opioids in this group of people should be considered. That would provide some insight into whether opioid prescribing appeared to improve or worsen health. Expanding on McCrorie's (2015) qualitative work (McCrorie et al. 2015), examining reasons for prescribing would also improve understanding of why opioid prescribing starts or continues despite the growing evidence of the harms caused (Baldini et al. 2012; Els et al. 2017; Stannard 2018; Taylor et al. 2019).

8.8 Study Conclusion

This study, which is the first of its kind in Wales, has revealed that opioid analgesic prescribing for non-cancer pain significantly increased in in the country between 2005 and 2015. Whilst weak opioid medicines accounted for most

prescriptions, prescribing rates for strong opioid analgesics such as morphine, oxycodone and fentanyl quadrupled over the period. Women received 50% more prescriptions than men and gender disparities were noted in overall opioid burden as well. Prescribing rates also rose with increasing age, which although seemingly expected due to higher levels of pain reporting with age, carries significant risk of harm in that population.

Prior to this study being undertaken, it was known the number of prescriptions for opioid analgesics being issued in Wales had hugely increased. However, the analyses presented here give much more detail on where and towards whom prescribing is directed. Primary care practice level data allows examination of prescribing trends but without the age, gender, and socioeconomic deprivation stratification this study presents. It is crucial to track prescribing trends, but the clinical application of the data is limited without being able to better identify those people most at risk, either due to dose, duration or associated demographic factors as has been done in this study.

This thesis proposes that current measures of prescribing are likely to underestimate the impact of opioid analgesic prescribing on the populace, either as a whole or specific sections of it. Estimated measures of oral morphine equivalence and prescribing persistence revealed a significant increase in opioid burden in the population over the 11 years of the study, which was not accounted for by prescribing rates alone. There is unlikely to be a perfect measure of prescribing, certainly not one that covers all medicines in all disease states. However, oral morphine equivalence measures are increasingly used in research and prescribing guidance, so finding a method of incorporating it into timely analysis would be prudent. The introduction of a variety of legislation and guidance during the study period did little to temper the rates of increase. It points towards a problem of dissemination and implementation of clinical guidelines. A lot of time is invested in developing policies and guidance but much less on how they will be adopted into practice or how compliance with them is measured. Welsh Government and Health Boards should exploit Wales being a

relatively small country as an advantage to developing better systems for sharing practice. There is no good reason that national pathways of care, timely monitoring systems easily accessed by practitioners and researchers and professional and public awareness campaigns cannot be used to raise the profile of pain and the problems with opioid analgesics.

Opioid prescribing has previously been associated with an increase in healthcare utilisation, but this thesis gives the first indication of how that affects people living in Wales. Prescribing is one of the main activities in primary care. This study observed 5 times more primary care interactions with people with pain-related diagnoses receiving opioid analgesic prescriptions compared to those with similar diagnosis but not receiving opioids. Even assuming some of the difference in numbers of visits in primary care were for the prescription itself, this does not explain the 3 times greater use of healthcare in other sectors also noted. Whilst pain services are available across Wales, the majority of people living with pain will not access them. Investment in training and education of healthcare professionals from all disciplines, moving services into Primary Care and working more closely with third sector organisations to improve access to non-medical support is likely to have more benefit to the population than just expanding existing pain service models.

From a public health perspective, what is likely to be of most concern, is the disproportionate opioid prescribing and consequent healthcare utilisation observed in areas of Wales with the highest levels of socioeconomic deprivation and predominating in the working age population. This points towards far greater pain prevalence in the most deprived areas, where higher than average levels of ill-health, obesity and low levels of activity are also observed. Strong opioid analgesics like morphine, oxycodone and fentanyl rose particularly sharply in these areas during the study period. The harms associated with opioid analgesics are likely to have a disproportionately negative effect over time in deprived areas, worsening prognosis and potentially maintaining the health and well-being disparities noted between them and wealthier areas. What seems

clear, having completed this research, is that guidelines alone are likely to be insufficient to reduce the use of opioid analgesics in Wales. The problem of opioid prescribing is linked to the problem of pain and how it is understood and managed within, and without healthcare. The perception that pain management is a specialty pursuit when, in fact, it is ubiquitous to all sections of healthcare, may be responsible in part for this.

Arising from this thesis are several suggestions for policy development to address opioid prescribing. Welsh Government policies are frequently aimed at reducing societal and health inequality but currently, prescribing guidelines, where available, do not differentiate between populations with disparate risks. Further research is also needed across the country to examine people's attitudes to pain and the use of opioid analgesics in that context. Factors which influence prescribing were not examined here, but based on previous studies, are often associated with a seeming lack of other safer, timely options to educate and support people presenting with pain. What must be guarded against however is using the lack of alternatives as a reason to continue prescribing opioid analgesics when they are not evidenced or there is no demonstrable benefit to those receiving them. Prescribers must be supported not to prescribe or to reduce and stop opioid analgesics which are causing harm, even when there is no alternative to offer. The sad truth is that for many long-term pain conditions, the 'right' answer, in terms of 'what makes this better?" is not known. It is clear however, that for many people, opioids are likely to be the wrong answer. Health Boards and other organisations including the Welsh Government must invest in public awareness campaigns to bring attention to the poor evidence for using opioid analgesics, especially in the long term and the additional health risks they can cause.

The reasons for disproportionate levels of opioid prescribing in areas with greater deprivation and the high rates of healthcare utilisation are complex and affect all countries in the UK. The research presented here, whilst focussed on Wales, corroborates the findings from around the UK where consistently

opioid analgesic prescribing is observed to be higher in areas of greater socioeconomic deprivation. Given the large dataset used for this study, it is not unreasonable to suggest the results could be generalised and a similar pattern of increased healthcare utilisation would be likely observed across the UK more widely, with significant cost implications to the NHS as a whole. The observation that prescribing rates increased rapidly in the least deprived areas of Wales also suggests a wider problem of growing pain prevalence and opioid prescribing that is less frequently discussed and warrants further investigation. There is no doubt that in the long-term, reducing socioeconomic disparity would have a great effect on general health and well-being, but it appears that opioid analgesic use is widespread throughout the population. Actions taken to improve the quality of prescribing and support services in one demographic would benefit the whole population. Greater levels of resource are undoubtedly required to address the concerns in the most deprived areas of Wales and the UK more widely. However, no population demographic should be assumed to be untouched by over-prescribing of opioids. Adding to the problem by continuing to prescribe medicines which are not enabling people to live better and more effective lives, or which result in greater healthcare need should be avoided regardless of individual circumstances.

It is hoped this thesis provides a base on which to build further research into the prescribing of opioids and other analgesics. It highlights the need to investigate what might underly disparities in prescribing whether due to geographical location, gender, age or socioeconomic deprivation. It suggests methods of monitoring prescribing opioid trends which may be more meaningful to prescribers and help practitioners and policy makers to get to grips with the burden opioids place upon the population. This research also signals that healthcare use might be influenced by opioid prescribing, which warrants more detailed exploration. Although only a small country, Wales looks to have quite a big problem with pain and prescribing. The advantage of being small however, is

that even a few people, willing to engage in the changes required, could make a big difference to population health.

"*It will be alright in the end and, if it's not alright, it's not the end."*
Mark Kermode

References

Abdallah, C.G. and Geha, P. 2017. Chronic Pain and Chronic Stress: Two Sides of the Same Coin? *Chronic Stress* 1, pp. 247054701770476–10. Available at: http://journals.sagepub.com/doi/10.1177/2470547017704763.

Abel, G.A. et al. 2016. Adjusted indices of multiple deprivation to enable comparisons within and between constituent countries of the UK including an illustration using mortality rates. *BMJ Open* 6(11), p. e012750. Available at: https://bmjopen.bmj.com/content/6/11/e012750.full.pdf.

Addis, S. et al. 2019. Implementing Prudent Healthcare in the NHS in Wales; what are the barriers and enablers for clinicians? *Journal of Evaluation in Clinical Practice* 25(1), pp. 104–110. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30144251&retmode=ref&cmd=prlinks.

Administrative Data Research UK 2021. Administrative Data Research UK. Available at: https://www.adruk.org [Accessed: 16 April 2021].

Aguera-Ortiz, L. et al. 2013. Unexplained pain complaints and depression in older people in primary care. *The Journal of Nutrition, Health & Aging* 17(6), pp. 574–577. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23732555&retmode=ref&cmd=prlinks.

Akbari, A. and Torabi, F. 2017. Personal communication - explanation of study matching. 21 March 2017

Alexander, J. et al. 2019. Assessing the Value of Time Series Real-World and Clinical Trial Data vs. Baseline-Only Data in Predicting Responses to Pregabalin Therapy for Patients with Painful Diabetic Peripheral Neuropathy. *Clinical Drug Investigation* 39(8), pp. 775–786. Available at: https://doi.org/10.1007/s40261-019-00812-6.

Alghamdi, S.S.A. et al. 2020. Prescribing trends over time by non-medical independent prescribers in primary care settings across Wales (2011-2018): a secondary database analysis. *BMJ open* 10(10), pp. e036379-8. Available at: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2019-036379.

Alho, H. et al. 2020. Opioid-related deaths in Europe: Strategies for a comprehensive approach to address a major public health concern. *The International journal on drug policy* 76, p. 102616. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0955395919303305.

Ali, A. et al. 2018. Managing Chronic Pain in the Elderly: An Overview of the Recent Therapeutic Advancements. *Cureus* 10(9), p. e3293. doi: 10.7759/cureus.3293.

All Wales Medicines Strategy Group 2013. National Prescribing Indicators 2013–2014. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-optimisation/national-prescribing-indicators/2013-2014/.

All Wales Medicines Strategy Group 2014. Polypharmacy: Guidance for Prescribing. Available at: https://awmsg.nhs.wales/files/guidelines-and-pils/polypharmacy-guidance-for-prescribing-pdf/ [Accessed: 14 November 2020].

All Wales Medicines Strategy Group 2021. All Wales Medicines Strategy Group: Prescribing Guidance. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-optimisation/prescribing-guidance/ [Accessed 24 July 2021]

All Wales Medicines Strategy Group and All Wales Therapeutics and Toxicology Centre 2020. Persistent Pain Resources. Available at: https://awttc.org/news/awmsg-resources-use-opioids-updated-account-mhra-drug-safety-updates.

All Wales Medicines Strategy Group. 2015. Polypharmacy: Guidance for Prescribing., pp. 1–36. Available at: https://awmsg.nhs.wales/files/guidelines-and-pils/polypharmacy-guidance-for-prescribing-pdf/.

All Wales Medicines Strategy Group. 2020. Persistent Pain Resources. Available at: https://awttc.org/news/awmsg-resources-use-opioids-updated-account-mhra-drug-safety-updates.

All Wales Prescribing Advisory Group 2021. *AWPAG minutes 17 Mar 21 - Final*. Available at: https://awmsg.nhs.wales/files/awpag-meetings/awpag-minutes-17-mar-21-pdf/.

All Wales Therapeutics and Toxicology Centre 2018. National prescribing indicators 2019-2020. Available at: https://www.awttc.org/national-prescribing-indicators-2019-2020 [Accessed: 12 August 2021].

All Wales Therapeutics and Toxicology Centre 2021. All Wales Therapeutics and Toxicology Centre. Available at: https://www.awttc.org [Accessed: 8 June 2021].

Amsterdam, J. van and Brink, W. van den 2015. The Misuse of Prescription Opioids: A Threat for Europe? *Current drug abuse reviews* 8(1), pp. 3–14. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26084418&retmode=ref&cmd=prlinks.

Andersson, H.I. 1994. The epidemiology of chronic pain in a Swedish rural area. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 3 Suppl 1(Suppl 1), pp. S19-26. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=7866366&retmode=ref&cmd=prlinks.

Andreu-Perez, J. et al. 2015. Big Data for Health. *IEEE Journal of Biomedical and Health Informatics* 19(4), pp. 1193–1208. doi: 10.1109/jbhi.2015.2450362.

Arul, J. and John, W. 2020. Basic Opioid Pharmacology - An Update. *British Journal of Pain* 14(2), pp. 115–121. Available at: https://pubmed.ncbi.nlm.nih.gov/32537150.

Ashaye, T. et al. 2018. Opioid prescribing for chronic musculoskeletal pain in UK primary care: results from a cohort analysis of the COPERS trial. *BMJ Open* 8(6), p. e019491. doi: 10.1136/bmjopen-2017-019491.

Asmundson, G.J.G. and Katz, J. 2009. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. *Depression and anxiety* 26(10), pp. 888–901. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19691031&retmode=ref&cmd=prlinks.

Atherton, F. and Welsh Government. 2019. Valuing our health: Chief Medical Officer's Annual Report 2018/19. Available at: https://gov.wales/sites/default/files/publications/2019-05/valuing-our-health.pdf.

Auditor General for Wales 2018. *A picture of primary care in Wales*. Wales Audit Office. Available at: https://www.audit.wales/system/files/publications/picture-of-primary-care-2018-english_0.pdf.

Australian Government Department of Health 2019. National Real Time Prescription Monitoring (RTPM). Available at: https://www.health.gov.au/initiatives-and-programs/national-real-time-prescription-monitoring-rtpm.

Aylward, M. et al. 2013. *Simply Prudent Healthcare - achieving better care and value for money in Wales - discussion paper*. Cardiff: Bevan Commission., p. 10. Available at: https://ctrtraining.co.uk/documents/BevanCommissionSimplyPrudentHealthcarev104122013.pdf

Ayres, I. and Jalal, A. 2018. The Impact of Prescription Drug Monitoring Programs on U.S. Opioid Prescriptions. *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine \& Ethics* 46(2), pp. 387–403. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30146997&retmode=ref&cmd=prlinks

Azevedo, L.F. et al. 2013. Chronic Pain and Health Services Utilization. *Medical care* 51(10), pp. 859–869. Available at: http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=107970643&site=ehost-live&scope=site&authtype=shib&custid=s8000044

Aziz, Q. et al. 2019. The IASP classification of chronic pain for ICD-11: chronic secondary visceral pain. *PAIN* 160(1), pp. 69–76. Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.9.aspx.

Baker, R. 2004. Implications of Harold Shipman for general practice. *Postgraduate Medical Journal* 80(944), pp. 303–6-- discussion 307--8. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=15192157&retmode=ref&cmd=prlinks.

Baldini, A. et al. 2012. A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide. *The primary care companion for CNS disorders* 14(3). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3466038/.

Ballantyne, J.C. 2003. Chronic pain following treatment for cancer: the role of opioids. *The oncologist* 8(6), pp. 567–575. doi: 10.1634/theoncologist.8-6-567.

Ballantyne, J.C. 2017. Opioids for the Treatment of Chronic Pain: Mistakes Made, Lessons Learned, and Future Directions. *Anesthesia and Analgesia* 125(5), pp. 1769–78. doi: 10.1213/ane<.0010000000002500.

Ballantyne, J.C. and Shin, N.S. 2008. Efficacy of Opioids for Chronic Pain: A Review of the Evidence. *Clinical Journal of Pain* 24(6), pp. 469–478.

Bambra, C. 2016. *Health Divides - Where you live can kill you*. Bristol: Bristol: Policy Press. Available at: https://policy.bristoluniversitypress.co.uk/health-divides.

Barnard, H. 2018. Poverty in Wales 2018., pp. 1–34. Available at: https://www.jrf.org.uk. [Accessed 9 September 2020]

BBC News 2018. NHS data breach affects 150,000 patients in England. Available at: https://www.bbc.co.uk/news/technology-44682369.

Bedard, N.A. et al. 2020. Optimum Designs for Large Database Research in Musculoskeletal Pain Management. *Journal of Bone and Joint Surgery* 102(Suppl 1), pp. 54–58. Available at: https://journals.lww.com/10.2106/JBJS.20<.00101.

Bedson, J. et al. 2016. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. *Pain* 157(7), pp. 1525–1531. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27003191&retmode=ref&cmd=prlinks.

Bekkering, G.E. et al. 2011. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. *Current medical research and opinion* 27(7), pp. 1477–1491. Available at: http://www.tandfonline.com/doi/full/10.1185/03007995.2011.586332.

Bennett, M.I. et al. 2019. The IASP classification of chronic pain for ICD-11: chronic cancer-related pain. *Pain* 160(1), p. 38. Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.5.aspx.

Benoliel, R. et al. 2019. The IASP classification of chronic pain for ICD-11: chronic secondary headache or orofacial pain. *Pain* 160(1). Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.8.aspx.

Benyamin, R. et al. 2008. Opioid complications and side effects. *Pain physician* 11(2 Suppl), pp. S105-20.

Berger, A. et al. 2012. Clinical characteristics and patterns of healthcare utilization in patients with painful neuropathic disorders in UK general practice: a retrospective cohort study. *BMC Neurology* 12(1), p. 8. Available at: https://doi.org/10.1186/1471-2377-12-8.

Bernal, J.L. et al. 2017. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *International journal of epidemiology* 46(1), pp. 348–355. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27283160&retmode=ref&cmd=prlinks.

Bevan, G. et al. 2014. *The Four Health Systems of the United Kingdom*. Health Foundation. Available at: http://books.google.co.uk/books?id=jszPvQEACAAJ&dq=intitle:The+four+health+systems+of+the+United+Kingdom+how+do+they+compare&hl=&cd=1&source=gbs_api.

Bialas, P. et al. 2020. Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and meta-analysis of open-label extension trials with a study duration ≥26 weeks. *European Journal of Pain* 24(2), pp. 265–278. doi: 10.1002/ejp.1496.

Black-Tiong, S. et al. 2021. Trends in long-term opioid prescriptions for musculoskeletal conditions in Australian general practice: a national longitudinal study using MedicineInsight,

2012–2018. *BMJ Open* 11(4), p. e045418. Available at: https://bmjopen.bmj.com/content/11/4/e045418.

Black, N. 1999. High-quality clinical databases: breaking down barriers. *The Lancet* 353(9160), pp. 1205–1206. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0140673699001087.

Blanch, B. et al. 2014. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *British Journal of Clinical Pharmacology* 78(5), pp. 1159–1166. Available at: http://doi.wiley.com/10.1111/bcp.12446.

Blozik, E. et al. 2009. Depression and anxiety as major determinants of neck pain: a cross-sectional study in general practice. *BMC Musculoskeletal Disorders* 10(1), p. 13. doi: 10.1186/1471-2474-10-13.

Blyth, F.M. and Schneider, C.H. 2018. Global burden of pain and global pain policy-creating a purposeful body of evidence. *Pain* 159 Suppl 1, pp. S43–S48. doi: 10.1097/j.pain<.0010000000001311.

Blyth, F.M. et al. 2019. The Global Burden of Musculoskeletal Pain-Where to From Here? *American Journal of Public Health* 109(1), pp. 35–40. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30495997&retmode=ref&cmd=prlinks.

Board of Community Health Councils in Wales. 2018. *Our lives on hold...* Cardiff: Community Health Councils of Wales. Available at: http://www.wales.nhs.uk/sitesplus/documents/899/Our%20lives%20on%20hold%20-%20ENGLISH%2010.05.20181.pdf.

Bobinac, A. et al. 2010. Willingness to pay for a quality-adjusted life-year: the individual perspective. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 13(8), pp. 1046–1055. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1098301511718381.

Bohensky, M.A. 2010. Data Linkage: A powerful research tool with potential problems. *BMC Health Services Research* 10(1), pp. 1–7. doi: 10.1186/1472-6963-10-346.

Bosetti, C. et al. 2019. Trends in the consumption of opioids for the treatment of severe pain in Europe, 1990–2016. *European Journal of Pain* 23(4), pp. 697–707. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/ejp.1337.

Boudreau, D. et al. 2009. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiology and Drug Safety* 18(12), pp. 1166–1175. Available at: http://doi.wiley.com/10.1002/pds.1833.

Bourgeais, V. and Krueger, A. 2017. *Eurostat newsrelease: 2015 GDP per capita in 276 EU regions*. Eurostat Press Office. Available at: https://ec.europa.eu/eurostat/documents/2995521/7962764/1-30032017-AP-EN.pdf/4e9c09e5-c743-41a5-afc8-eb4aa89913f6.

Bowsher, D. et al. 1991. Prevalence of chronic pain in the British population : a telephone survey of 1037 households. *Pain Clinic* 4, pp. 223–230.

Bozic, K.J. et al. 2012. Resource utilization and costs before and after total joint arthroplasty. *BMC Health Services Research* 12(73). Available at: https://link.springer.com/content/pdf/10.1186/1472-6963-12-73.pdf.

Braden, J.B. et al. 2010. Emergency Department Visits Among Recipients of Chronic Opioid Therapy. *Archives of Internal Medicine* 170(16), pp. 1425–1432. doi: 10.1001/archinternmed.2010.273.

Bradley, P. et al. 2014. *Achieving prudent healthcare in NHS Wales*. Public Health Wales. Available at: https://pureadmin.uhi.ac.uk/ws/portalfiles/portal/1921669/Achieving_prudent_healthcare_in_NHS_Wales_paper_Revised_version_FINAL_.pdf.

Brady, J.E. et al. 2017. Risk markers for fatal and non-fatal prescription drug overdose: a meta-analysis. *Injury epidemiology* 4(1), p. 24. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=28762157&retmode=ref&cmd=prlinks.

Braveman, P. and Gottlieb, L. 2014. The social determinants of health: it's time to consider the causes of the causes. *Public health reports (Washington, D.C. : 1974)* 129 Suppl 2(1_suppl2), pp. 19–31. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3863696/#__ffn_sectitle.

Breivik, H. and Stubhaug, A. 2014. Burden of disease is often aggravated by opioid treatment of chronic pain patients: Etiology and prevention. *Pain* 155(12), pp. 2441–2443. Available at: http://journals.lww.com/00006396-201412000-00002.

Breivik, H. et al. 2006. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain* 10(4), pp. 287–287. doi: 10.1016/j.ejpain.2005.06.009.

Breivik, H. et al. 2013. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health* 13(1), pp. 1–29. Available at: http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-13-1229.

Brena, S.F. and Sanders, S.H. 1992. Chronic pain: fix or manage? *Clinical Journal of Pain* 8(2), pp. 172–7.

Brew, B. et al. 2016. The health and wellbeing of Australian farmers: a longitudinal cohort study. *BMC Public Health* 16(1), pp. 1–11. Available at: http://dx.doi.org/10.1186/s12889-016-3664-v.

Brouwer, W.B.F. et al. 2008. Welfarism vs. extra-welfarism. *Journal of health economics* 27(2), pp. 325–338. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18179835&retmode=ref&cmd=prlinks.

Bruggenjurgen, B. et al. 2007. Utilisation of medical resources of patients with pain undergoing an outpatient opioid therapy. *Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany))* 69(6), pp. 353–358. doi: 10.1055/s-2007-981679.

Brummett, C.M. et al. 2019. Health Care Burden Associated with Outpatient Opioid Use Following Inpatient or Outpatient Surgery. *Journal of Managed Care & Specialty Pharmacy* 25(9), pp. 973–983. doi: 10.18553/jmcp.2019.19055.

Buchbinder, R. et al. 2013. Placing the global burden of low back pain in context. *Best Practice & Research Clinical Rheumatology* 27(5), pp. 575–589. doi: 10.1016/j.berh.2013.10.007.

Butler, J.M. et al. 2018. Big Data and the Opioid Crisis: Balancing Patient Privacy with Public Health. *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine \& Ethics* 46(2), pp. 440–453. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30146994&retmode=ref&cmd=prlinks.

Byrne, M. et al. 2003. Frequent attenders to an emergency department: A study of primary healthcare use, medical profile, and psychosocial characteristics. *Annals of emergency medicine* 41(3), pp. 309–318. doi: 10.1067/mem.2003.68.

Calderwood, C. 2017. *Realising Realistic Medicine: Chief Medical Officer for Scotland annual report 2015-2016*. Edinburgh: Healthcare Quality and Improvement Directorate, Scottish Government. Available at: https://www.gov.scot/publications/chief-medical-officer-scotland-annual-report-2015-16-realising-realistic-9781786526731/.

Campbell, G. et al. 2015. The Pain and Opioids IN Treatment study: characteristics of a cohort using opioids to manage chronic non-cancer pain. *Pain* 156(2), pp. 231–242. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25599444&retmode=ref&cmd=prlinks.

Carlisle, D. 2017. Prescription charges backfire on UK health and wealth. Available at: https://www.pharmaceutical-journal.com/news-and-analysis/prescription-charges-backfire-on-uk-health-andnbspwealth/20203213.article?firstPass=false.

Carr, D.B. and Goudas, L.C. 1999. Acute Pain. *The Lancet* 353(9169), pp. 2051–2058. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(99)03313-9/fulltext.

Centers for Disease Control and Prevention 2016. CDC guideline for prescribing opioids for chronic pain—United States, 2016. Available at: http://scholar.google.comjavascript:void(0).

Centers for Disease Control and Prevention 2020. America's Drug Overdose Epidemic: Putting data to action. Available at: https://www.cdc.gov/injury/features/prescription-drug-overdose/index.html [Accessed: December 2020].

Centers for Disease Control and Prevention 2021. Opioid overdose: US Opioid Dispensing Rate Maps. Available at: https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html.

Centers for Disease Control and Prevention 2021. Opioid Overdose. Available at: https://www.cdc.gov/drugoverdose/epidemic/index.html [Accessed: 26 June 2021].

Centers for Disease Control and Prevention 2021. Prescription Drug Monitoring Programs (PDMPs). Available at: https://www.cdc.gov/drugoverdose/pdmp/states.html [Accessed: January 2021].

Centre for Clinical Practice at National Institute for Health and Care Excellence . 2013. Neuropathic Pain: The Pharmacological Management of Neuropathic Pain in Adults in Non-specialist Settings. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25577930&retmode=ref&cmd=prlinks.

Chan, B.T. et al. 2005. Factors influencing family physicians to enter rural practice: Does rural or urban background make a difference? *Canadian Family Physician* 51, pp. 1246–1247. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1479469/pdf/jCFP_v051_pg1247.pdf.

Chang, H.-Y. et al. 2016. Impact of prescription drug monitoring programs and pill mill laws on high-risk opioid prescribers: A comparative interrupted time series analysis. *Drug and alcohol dependence* 165, pp. 1–8. doi: 10.1016/j.drugalcdep.2016.04.033.

Chang, H.-Y. et al. 2018. Healthcare costs and utilization associated with high-risk prescription opioid use: a retrospective cohort study. *BMC Medicine* 16(69). doi: https://doi.org/10.1186/s12916-018-1058-y.

Chaparro, L.E. et al. 2013. Opioids compared to placebo or other treatments for chronic low-back pain. *The Cochrane Database of Systematic Reviews* . Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004959.pub4/pdf.

Chaparro, L.E. et al. 2014. Opioids Compared with Placebo or Other Treatments for Chronic Low Back Pain. *Spine* 39(7), pp. 556–563. doi: 10.1097/brs<.0010000000000249.

Chapman, C.R. et al. 2010. Opioid Pharmacotherapy for Chronic Non-Cancer Pain in the United States: A Research Guideline for Developing an Evidence-Base. *Journal of pain : official journal of the American Pain Society.* 11(9).

Che, Z. et al. 2017. Deep Learning Solutions for Classifying Patients on Opioid Use. *AMIA ... Annual Symposium proceedings. AMIA Symposium* 2017, pp. 525–534. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29854117&retmode=ref&cmd=prlinks.

Chen, T.-C. et al. 2019. Impact of tramadol classification on the prescribing of other pain medicines commonly related to drug-misuse deaths in UK. *Pharmacoepidemiology and Drug Safety* 28, pp. 253–253. Available at: http://gateway.webofknowledge.com/gateway/Gateway.cgi?GWVersion=2&SrcAuth=mekentosj&SrcApp=Papers&DestLinkType=FullRecord&DestApp=WOS&KeyUT=000481785601272.

Chevalier, P. et al. 2014. A description of clinical characteristics and treatment patterns observed within prescribed opioid users in Germany and the UK. *Pain Management* 4(4), pp. 267–76. doi: https://doi.org/10.2217/pmt.14.26.

Chief Medical Officer of England 2009. *150 years of the Annual Report of the Chief Medical Officer*. London: Department of Health (England)., p. 70. Available at: https://webarchive.nationalarchives.gov.uk/ukgwa/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_096231.pdf.

Chou, R. et al. 2009. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The Journal of Pain* 10(2), pp. 113–130. Available at: https://pubmed.ncbi.nlm.nih.gov/19187889.

Cicero, T.J. et al. 2007. Trends in the use and abuse of branded and generic extended-release oxycodone and fentanyl products in the United States. *Drug and alcohol dependence* 91(2–3), pp. 115–120. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17590285&retmode=ref&cmd=prlinks.

Claxton, K. et al. 2015. Causes for concern: Is NICE failing to uphold its responsibilities to all NHS patients? *Health Economics* 24, pp. 1–7. Available at: https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/hec.3130.

Clinical Practice Research Datalink (CPRD). 2021. Available at: https://www.cprd.com/ [Accessed: February 2021].

Coast, J. et al. 2008. Welfarism, extra-welfarism and capability: the spread of ideas in health economics. *Social Science & Medicine* 67(7), pp. 1190–1198. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18657346&retmode=ref&cmd=prlinks.

Cohen, S.P. et al. 2008. The Effect of Opioid Dose and Treatment Duration on the Perception of a Painful Standardized Clinical Stimulus. *Regional anesthesia and pain medicine* 33(3), pp. 199–206. Available at: https://rapm.bmj.com/lookup/doi/10.1016/j.rapm.2007.10.009.

Coll, M.-P. et al. 2012. The role of gender in the interaction between self-pain and the perception of pain in others. *The Journal of Pain* 13(7), pp. 695–703. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1526590012006207.

Collett, B. et al. 2011. *IASP Task force on wait times: Summary and recommendations*. International Association for the Study of Pain. Available at: https://www.iasp-pain.org/wp-content/uploads/2021/07/IASP-Recommendations-for-Wait-Times-for-Treatment-of-Pain.pdf.

Collett, B.J. 2001. Chronic opioid therapy for non-cancer pain. *BJA: British Journal of Anaesthesia* 87(1), pp. 133–143. doi: 10.1093/bja/87.1.133.

Colvin, L.A. et al. 2019. Postoperative pain management and opioids 3 Perioperative opioid analgesia—when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *The Lancet* 393(10180), pp. 1558–1568. Available at: http://dx.doi.org/10.1016/S0140-6736(19)30430-1.

Compton, W.M. et al. 2015. Prescription opioid abuse: Problems and responses. *Preventive Medicine* 80, pp. 5–9. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0091743515001036.

Connelly, D. 2020. Some patients with chronic pain face waiting years to see a specialist - The Pharmaceutical Journal. *The Pharmaceutical Journal* February 2020. Available at: https://pharmaceutical-journal.com/article/news/some-patients-with-chronic-pain-face-waiting-years-to-see-a-specialist.

Cooney, M.A. et al. 2013. Current Knowledge of Pain After Breast Cancer Treatment: A Systematic Review. *Pain Management Nursing* 14(2), p. 110. Available at: https://doi.org/10.1016/j.pmn.2010.09.002.

Corran, T.M. et al. 1997. The classification of patients with chronic pain: age as a contributing factor. *The Clinical Journal of Pain* 13(3), pp. 207–214. Available at: http://journals.lww.com/00002508-199709000-00005.

Coyle, D.T. et al. 2018. Opioid analgesic dose and the risk of misuse, overdose, and death: A narrative review. *Pharmacoepidemiology and Drug Safety* 27(5), pp. 464–472. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29243305&retmode=ref&cmd=prlinks.

Crisp, R. et al. 2009. *Work and worklessness in deprived neighbourhoods: Policy assumptions and personal experiences*. Joseph Rowntree Foundation., p. 45. Available at: https://www.basw.co.uk/system/files/resources/basw_10124-1_0.pdf.

Cross, M. et al. 2014. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases* 73(7), pp. 1316–1322. doi: 10.1136/annrheumdis-2013-204627.

Currow, D.C. et al. 2016. Using opioids in general practice for chronic non-cancer pain: an overview of current evidence. *The Medical Journal of Australia* 204(8), pp. 1–7. Available at: http://dx.doi.org/10.5694/mja16<.00166.

Curtis, H.J. and Goldacre, B. 2018. OpenPrescribing: normalised data and software tool to research trends in English NHS primary care prescribing 1998–2016. *BMJ open* 8(2), pp. e019921-10. Available at: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2017-019921.

Curtis, H.J. et al. 2019. Opioid prescribing trends and geographical variation in England, 1998–2018: a retrospective database study. *The Lancet Psychiatry* 6(2), pp. 140–150. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30580987&retmode=ref&cmd=prlinks.

Curtis, L. and Burns, A. 2015. *Unit Costs of Health and Social Care 2015*. Canterbury: Personal Social Services Research Unit, University of Kent. Available at: https://www.pssru.ac.uk/pub/uc/uc2015/full.pdf.

Dance, A. 2019. THE PAIN GAP. *Nature* 567, pp. 448–450.

Daniels, J. et al. 2017. Better safe than sorry? Frequent attendance in a hospital emergency department: an exploratory study. *British Journal of Pain* 12(1), pp. 10–19. doi: 10.1177/2049463717720635.

Dao, T.T. and LeResche, L. 2000. Gender differences in pain. *Journal of Orofacial Pain* 14(3), pp. 169–84-- discussion 184--95. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=11203754&retmode=ref&cmd=prlinks.

Darnall, B.D. et al. 2012. Medical and Psychological Risks and Consequences of Long-Term Opioid Therapy in Women. *Pain Medicine* 13(9), pp. 1181–1211. Available at: https://academic.oup.com/painmedicine/article-pdf/13/9/1181/5276347/13-9-1181.pdf.

Dash, S. et al. 2019. Big data in healthcare: management, analysis and future prospects. *Journal of Big Data* 6(1), pp. 1–25. Available at: https://doi.org/10.1186/s40537-019-0217-0.

Datapharm Ltd 2021. Electronic Medicines Compendium. Available at: https://www.medicines.org.uk/emc [Accessed: 2021].

Davies, E. et al. 2018. Examining patterns in opioid prescribing for non-cancer related pain in wales: preliminary data from a retrospective cross-sectional study using large datasets. *British Journal of Pain* 13(3), pp. 145–158. doi: 10.1177/2049463718800737.

De Mauro, A. et al. 2016. A formal definition of Big Data based on its essential features. *Library Review* 65(3), pp. 122–135. Available at: https://www.emerald.com/insight/content/doi/10.1108/LR-06-2015-0061/full/html.

Degenhardt, L. et al. 2016. The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. *Pharmacoepidemiology and Drug Safety* 25(5), pp. 521–538. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26781123&retmode=ref&cmd=prlinks.

Delamothe, T. 2008. Founding principles. *British Medical Journal* 336(7655), pp. 1216–1218. Available at: https://www.bmj.com/lookup/doi/10.1136/bmj.39582.501192.94.
Demos, K. et al. 2013. Does Farming Have an Effect on Health Status? A Comparison Study in West Greece. *International Journal of Environmental Research and Public Health* 10(3), pp. 776–792. Available at: http://www.mdpi.com/1660-4601/10/3/776.

Department of Health 2012. *Long Term Conditions Compendium: Third Edition*. Department of Health., pp. 1–53. Available at: http://www.innspub.net/wp-content/uploads/2013/12/IJB-V4No1-p158-166.pdf.

Department of Health 2021. The Misuse of Drugs and the Misuse of Drugs (Supply to Addicts) (Amendment) Regulations 2005. Available at: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Prescriptions/DH_4123320.

Department of Health and Social Care. 2015. NHS reference costs 2014 to 2015. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.

Desai, R.J. et al. 2015. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. *BMJ* 350(may14 1), p. h2102. Available at: https://www.bmj.com/content/350/bmj.h2102.

Devulder, J. et al. 2005. Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain. *Current medical research and opinion* 21(10), pp. 1555–1568. Available at: https://www.tandfonline.com/doi/abs/10.1185/030079905X65321.

Dhalla, I.A. et al. 2011. Facing up to the prescription opioid crisis. *BMJ* 343(aug23 1), p. d5142. Available at: https://www.bmj.com/content/343/bmj.d5142.

Digital Health and Care Wales 2021. PEDW Data Online. Available at: https://dhcw.nhs.wales/information-services/welsh-data-hub/pedw-data-online/ [Accessed: 25 April 2020].

Dillie, K.S. et al. 2008. Quality of Life Associated with Daily Opioid Therapy in a Primary Care Chronic Pain Sample. *Journal of American Board of Family Medicine* 21(2), pp. 108–117. doi: 10.3122/jabfm.2008.02.070144.

Dobbin, M. and Liew, D.F. 2020. Real-time prescription monitoring: helping people at risk of harm. *Australian Prescriber* 43(5), pp. 164–167. Available at: https://www.nps.org.au/australian-prescriber/articles/real-time-prescription-monitoring-helping-people-at-risk-of-harm.

Docking, R.E. et al. 2011. Epidemiology of back pain in older adults: prevalence and risk factors for back pain onset. *Rheumatology (Oxford, England)* 50(9), pp. 1645–1653. Available at: http://www.rheumatology.oxfordjournals.org/cgi/doi/10.1093/rheumatology/ker175.

Doidge, J. et al. 2020. Quality assessment in data linkage. Available at: https://www.gov.uk/government/publications/joined-up-data-in-government-the-future-of-data-linking-methods/quality-assessment-in-data-linkage.

Donovan, O. 2018. State of Wales. Available at: https://stateofwales.com/2018/10/the-welsh-economy-ii-an-economic-history-of-wales-in-brief/ [Accessed: 2 January 2021].
Dormuth, C.R. et al. 2012. Effect of a centralized prescription network on inappropriate prescriptions for opioid analgesics and benzodiazepines. *Canadian Medical Association Journal* 184(16), pp. E852–E856. Available at: https://www.cmaj.ca/content/184/16/E852.short.

Dowell, D. et al. 2016. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR. Recommendations and Reports* 65(1), pp. 1–49. doi: 10.15585/mmwr.rr6501e1er.

Dowell, D. et al. 2016. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 315(15), pp. 1624–1645.

Dunlop, W. et al. 2012. Quality of life benefits and cost impact of prolonged release oxycodone/naloxone versus prolonged release oxycodone in patients with moderate-to-severe non-malignant pain and opioid-induced constipation: a UK cost-utility analysis. *Journal of Medical Economics* 15(3), pp. 564–575. Available at: https://doi.org/10.3111/13696998.2012.665279.

Dunn, K.M. et al. 2010. Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. *Annals of Internal Medicine* 152(2), pp. 85–92. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3000551/pdf/ukmss-32216.pdf.

Dyer, C. 2004. Shipman inquiry recommends tighter rules on controlled drugs. *BMJ* 329(7459), p. 188. Available at: https://www.bmj.com/content/329/7459/188.3.

Dzierżanowski, T. and Ciałkowska-Rysz, A. 2017. Accessibility of opioid analgesics and barriers to optimal chronic pain treatment in Poland in 2000–2015. *Supportive Care in Cancer* 25(3), pp. 1–7. Available at: http://dx.doi.org/10.1007/s00520-016-3460-3.

EBM DataLab. 2017. OpenPrescribing.net 4.7.2: Opioid analgesics. Available at: https://openprescribing.net/bnf/040702/ [Accessed: 17 August 2021].

Eccleston, C. 2011. A normal psychology of chronic pain. *Psychologist* 24(6), pp. 422–425. Available at: https://www.scopus.com/inward/record.uri?partnerID=HzOxMe3b&scp=79959187272&origin=inward.

Eccleston, C. et al. 2021. Pragmatic but flawed: the NICE guideline on chronic pain. *Lancet* 397. Available at: www.thelancet.com.

Economics Observatory2020. How is coronavirus affecting the Welsh economy? - Economics Observatory. Available at: https://www.economicsobservatory.com/how-coronavirus-affecting-welsh-economy [Accessed: April 2021].

El-Ansary, M.S. and Galiongy, P. 1984. The history of pain relief by the ancient Egyptians. *Pain* 18(2), p. S34. doi: 10.1016/0304-3959(84)90184-2.

Elliott, A.M. et al. 2002. The course of chronic pain in the community: results of a 4-year follow-up study. *Pain* 99(1–2), pp. 299–307. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=12237208&retmode=ref&cmd=prlinks.

Els, C. et al. 2017. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *The Cochrane database of systematic reviews* 10(10), p. CD012509. Available at:

http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29084357&retmode=ref&cmd=prlinks.

Engel, G.L. 1959. Psychogenic pain and pain-prone patient. *The American journal of medicine* 26(6), pp. 899–918. Available at: https://www.amjmed.com/article/0002-9343(59)90212-8/pdf.

Engel, G.L. 1977. The need for a new medical model: A challenge for biomedicine. *Science* 196(4286), pp. 1–9.

Enke, O. et al. 2018. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: A systematic review and meta-analysis. *Canadian Medical Association Journal* 190(26), pp. E786–E793. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29970367&retmode=ref&cmd=prlinks.

European Commission 2018. *The EU Data Protection Reform and Big Data*. Available at: https://op.europa.eu/en/publication-detail/-/publication/51fc3ba6-e601-11e7-9749-01aa75ed71a1.

European Monitoring Centre for Drugs and Drug Addiction. 2020. *European Drug Report 2020: Trends and Developments*. Luxembourg: Publications Office of the European Union. Available at: https://www.emcdda.europa.eu/system/files/publications/13236/TDAT20001ENN_web.pdf.

Everdingen, M.H.J. van den B. et al. 2013. Prolonged QT interval by methadone: Relevance for daily practice? A prospective study in patients with cancer and noncancer pain. *Journal of Opioid Management* 9(4). doi: https://doi.org/10.5055/jom.2013.0167.

Expenditure Policy Division et al. 1998. *IMF Conference on Economic Policy and Equity--Issues Paper.pdf*. Washington, USA: International Monetary Fund. Available at: https://www.imf.org/external/np/fad/equity/issues.htm.

Faculty of Pain Medicine of the Royal College of Anaesthetists 2021. Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. Available at: https://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware [Accessed: 24 January 2021].

Faculty of Pain Medicine of the Royal College of Anaesthetists 2020. FPM guidance on resumption of pain services following disruption by the COVID-19 pandemic. Available at: https://fpm.ac.uk/covid-19-fpm-guidance-resumption-pain-services.

Faculty of Pain Medicine of the Royal College of Anaesthetists 2021. FPM concerns regarding new NICE Chronic Pain Guidelines. Available at: https://fpm.ac.uk/fpm-concerns-regarding-new-nice-chronic-pain-guidelines. [Accessed: 3 May 2021].

Faculty of Pain Medicine of the Royal College of Anaesthetists 2021. *Core Standards for Pain Management Services in the UK*. London: RCoA. Available at: https://fpm.ac.uk/sites/fpm/files/documents/2021-07/FPM-Core-Standards-2021_1.pdf.

Falk, M. et al. 2012. *A first course on Time Series Analysis: Examples with SAS*. Berlin: Druck und Verlag: epubli GmbH. Available at: http://books.google.co.uk/books?id=kTjQMRIa0ssC&printsec=frontcover&dq=intitle:A+First+Course+on+Time+Series+Analysis&hl=&cd=1&source=gbs_api [Accessed: 4 February 2020].

Fasick, V. et al. 2015. The hippocampus and TNF: Common links between chronic pain and depression. *Neuroscience and biobehavioral reviews* 53, pp. 139–159. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0149763415000883.

Favaretto, M. et al. 2020. What is your definition of Big Data? Researchers' understanding of the phenomenon of the decade. *PloS one* 15(2), pp. e0228987-20. Available at: https://dx.plos.org/10.1371/journal.pone.0228987.

Fayaz, A. et al. 2016. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ open* 6(6), p. e010364. doi: 10.1136/bmjopen-2015-010364. Available at: https://bmjopen.bmj.com/content/6/6/e010364.abstract.

Fehrmann, E. et al. 2019. The impact of age and gender on the ICF-based assessment of chronic low back pain. *Disability and Rehabilitation* 41(10), pp. 1190–1199. Available at: https://doi.org/10.1080/09638288.2018.1424950.

Fetene, D.M. et al. 2020. The impact of Victoria's real time prescription monitoring system (SafeScript) on a cohort of people who inject drugs. *The Medical Journal of Australia* 213(3), pp. 141–2. Available at: https://onlinelibrary.wiley.com/doi/abs/10.5694/mja2.50659.

Field, A. 2014. *Discovering Statistics using IBM SPSS Statistics 5e + SPSS 24*. SAGE Publications, Incorporated. Available at: http://books.google.co.uk/books?id=JQhSvQEACAAJ&dq=inauthor:andy+field+discovering+statistics&hl=&cd=7&source=gbs_api.

Fillingim, R. and Gear, R. (2004) "Sex differences in opioid analgesia: clinical and experimental findings," *European Journal of Pain*, 8(5), pp. 413–425. doi:10.1016/j.ejpain.2004.01.007. Available at: https://pubmed.ncbi.nlm.nih.gov/15324773/.

Fillingim, R.B. et al. 2005. Morphine responses and experimental pain: sex differences in side effects and cardiovascular responses but not analgesia. *The Journal of Pain* 6(2), pp. 116–124. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=15694878&retmode=ref&cmd=prlinks.

Finestone, H.M. et al. 2016. Opioid prescribing is a surrogate for inadequate pain management resources. *Canadian Family Physician* 62(6), pp. 465–468. Available at: http://www.cfp.ca/content/62/6/465.full.

Fink, D.S. et al. 2018. Association Between Prescription Drug Monitoring Programs and Nonfatal and Fatal Drug Overdoses. *Annals of internal medicine* 168(11), pp. 783–790. Available at: https://www.acpjournals.org/doi/10.7326/M17-3074.

Fischer, B. et al. 2014. Non-medical use of prescription opioids and prescription opioid-related harms: Why so markedly higher in North America compared to the rest of the world? *Addiction (Abingdon, England)* 109(2), pp. 177–181. Available at: http://doi.wiley.com/10.1111/add.12224.

Fischer, B. et al. 2014. Trends and changes in prescription opioid analgesic dispensing in Canada 2005-2012: an update with a focus on recent interventions. *BMC Health Services Research* 14(1), pp. 1–8.

Fischer, B. et al. 2016. Depression - A major but neglected consequence contributing to the health toll from prescription opioids? *Psychiatry research* 243, pp. 331–334. doi: 10.1016/j.psychres.2016.06.053.

Fischer, L. et al. 2007. The protective role of testosterone in the development of temporomandibular joint pain. *The Journal of Pain* 8(5), pp. 437–442. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17360240&retmode=ref&cmd=prlinks.

Ford, D.V. et al. 2009. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Services Research* 9, p. 157. doi: 10.1186/1472-6963-9-157.

Foy, R. et al. 2016. Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. *BMJ Open* 6(5), p. e010276. Available at: https://bmjopen.bmj.com/content/6/5/e010276.

Francis, K. 2021. *Personal Communication.* Pain service provision data and plans for the future. August 2021.

Franklin, G.M. and American Association of Neurology 2014. Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology. *Neurology* 83(14), pp. 1277–1284. doi: 10.1212/wnl<.0010000000000839.

Franklin, G.M. et al. 2012. Bending the prescription opioid dosing and mortality curves: Impact of the Washington State opioid dosing guideline. *American Journal of Industrial Medicine* 55(4), pp. 325–331. doi: 10.1002/ajim.21998.

Fredheim, O.M.S. et al. 2010. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway. *European Journal of Pain* 14(3), pp. 289–294. Available at: http://doi.wiley.com/10.1016/j.ejpain.2009.05.006.

Fullerton, E.F. et al. 2018. Impact of sex on pain and opioid analgesia: a review. *Current opinion in behavioral sciences* 23, pp. 183–190. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30906823&retmode=ref&cmd=prlinks.

Furlan, A.D. et al. 2006. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *Canadian Medical Association Journal* 174(11), pp. 1589–1594. doi: 10.1503/cmaj.051528.

Furlan, A.D. et al. 2011. A Comparison between Enriched and Nonenriched Enrolment Randomized Withdrawal Trials of Opioids for Chronic Noncancer Pain. *Pain Research and Management* 16(5), pp. 337–351. doi: 10.1155/2011/465281.

Galama, T.J. and Kippersluis, H. van 2018. A Theory of Socio-economic Disparities in Health over the Life Cycle. *The Economic Journal* 129(617), pp. 338–374. Available at: https://doi.org/10.1111/ecoj.12577.

Gallagher, R.M. 2006. Empathy: A Timeless Skill for the Pain Medicine Toolbox. *Pain Medicine* 7(3), pp. 213–214. doi: 10.1111/j.1526-4637.2006.00163.x.

Gatchel, R.J. et al. 2007. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological bulletin* 133(4), pp. 581–624. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17592957&retmode=ref&cmd=prlinks.

Gazelka, H.M. et al. 2020. Opioids in Older Adults: Indications, Prescribing, Complications, and Alternative Therapies for Primary Care. *Mayo Clinic proceedings* 95(4), pp. 793–800. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0025619620301452.

Ghoshal, M. et al. 2020. Chronic Noncancer Pain Management and Systemic Racism: Time to Move Toward Equal Care Standards. *Journal of pain research* 13, pp. 2825–2836. Available at: https://www.dovepress.com/chronic-noncancer-pain-management-and-systemic-racism-time-to-move-tow-peer-reviewed-fulltext-article-JPR.

Gibson, S.J. and Farrell, M. 2004. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. *The Clinical journal of pain* 20(4), pp. 227–239. Available at: http://journals.lww.com/00002508-200407000-00004.

Gibson, S.J. and Helme, R.D. 2001. Age-related differences in pain perception and report. *Clinics in geriatric medicine* 17(3), pp. 433–456. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0749069005700793.

Gibson, S.J. and Lussier, D. 2012. Prevalence and relevance of pain in older persons. *Pain medicine (Malden, Mass.)* 13 Suppl 2(suppl 2), pp. S23-6. Available at: https://academic.oup.com/painmedicine/article-lookup/doi/10.1111/j.1526-4637.2012.01349.x.

Gifford, L.S. and Butler, D.S. 1997. The Integration of Pain Sciences in Clinical Practice. *Journal of Hand Therapy* 10(2), pp. 86–95. Available at: https://reader.elsevier.com/reader/sd/pii/S0894113097800634?token=29D597C6677F73C9DEE30A0B44ACB066573115BDFDEF6365046AA8FD69D4AA2909DE13DA3A40B6E6C576DD49EB6CCAB6&originRegion=eu-west-1&originCreation=20210626102920.

Gilbert, S. et al. 2014. The Scottish model for chronic pain management services. *British Journal of Healthcare Management* 20(12), pp. 1–11.

Gisev, N. et al. 2016. Initiation of strong prescription opioids in Australia: cohort characteristics and factors associated with the type of opioid initiated. *British Journal of Clinical Pharmacology* 82(4), pp. 1–40. Available at: http://doi.wiley.com/10.1111/bcp.13026.

Glenn, S. 2021. Familywise Error Rate. Available at: https://www.statisticshowto.com/familywise-error-rate/ [Accessed: 9 March 2020].

Gomes, T. et al. 2011. Opioid dose and drug-related mortality in patients with non-malignant pain. *Archives of Internal Medicine* 171(7), pp. 686–691. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21482846&retmode=ref&cmd=prlinks.

Gomes, T. et al. 2014. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: a time series analysis. *CMAJ open* 2(4), pp. E256-61. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25485251&retmode=ref&cmd=prlinks. doi: 10.9778/cmajo.20140027

Gomes, T. et al. 2017. Changes in the dispensing of opioid medications in Canada following the introduction of a tamper-deterrent formulation of long-acting oxycodone: a time series analysis. *CMAJ open* 5(4), pp. E800–E807. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29167237&retmode=ref&cmd=prlinks.

González-Roldán, A.M. et al. 2020. Age-Related Changes in Pain Perception Are Associated with Altered Functional Connectivity During Resting State. *Frontiers in Aging Neuroscience* 12, pp. 11–10. Available at: https://www.frontiersin.org/article/10.3389/fnagi.202.00116/full.

Gordon, K. et al. 2017. Barriers to self-management of chronic pain in primary care: a qualitative focus group study. *The British journal of general practice : the journal of the Royal College of General Practitioners* 67(656), pp. e209–e217. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27993899&retmode=ref&cmd=prlinks.

Gosport Independent Panel 2018. The Panel Report - 20th June 2018. Available at: https://www.gosportpanel.independent.gov.uk/panel-report/ [Accessed: 11 September 2020].

Green, K. et al. 2019. Prescribing trends of gabapentin, pregabalin, and oxycodone: a secondary analysis of primary care prescribing patterns in England. *bjgpopen.org* 3(3), p. bjgpopen19X101662-10. doi: 10.3399/bjgpopen19x101662.

Greenfield, G. et al. 2016. Rethinking primary care's gatekeeper role. *British Medical Journal* 354, p. i4803. Available at: https://www.bmj.com/content/354/bmj.i4803.abstract.

Greenfield, G. et al. 2020. Frequent attendances at emergency departments in England. *Emergency medicine journal : EMJ* 37(10), pp. 597–599. doi: 10.1136/emermed-2018-208189.

Greenspan, J.D. et al. 2007. Studying sex and gender differences in pain and analgesia: A consensus report. *PAIN* 132(Supplement 1), pp. S26–S45. doi: 10.1016/j.pain.2007.10.014.

Grichnik, K.P. and Ferrante, F.M. 1991. The difference between acute and chronic pain. *The Mount Sinai journal of medicine, New York* 58(3), pp. 217–220. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=1875958&retmode=ref&cmd=prlinks.

Groves, S. et al. 2010. Abolition of prescription charges in Wales: the impact on medicines use in those who used to pay. *The International journal of pharmacy practice* 18(6), pp. 332–340. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21054593&retmode=ref&cmd=prlinks.

Gulliford, M. 2020. Opioid use, chronic pain and deprivation. *EClinicalMedicine* 21, p. 100341. Available at: https://linkinghub.elsevier.com/retrieve/pii/S2589537020300857.

Gureje, O. et al. 1998. Persistent Pain and Well-being. *JAMA* 280(2), pp. 147–151. Available at: https://jamanetwork.com/journals/jama/articlepdf/187723/joc72070.pdf.

Gustavsson, A. et al. 2012. Pharmaceutical treatment patterns for patients with a diagnosis related to chronic pain initiating a slow-release strong opioid treatment in Sweden. *Pain* 153(12), pp. 2325–2331. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=22944610&retmode=ref&cmd=prlinks.

Gustavsson, A. et al. 2012. Socio-economic burden of patients with a diagnosis related to chronic pain – Register data of 840,000 Swedish patients. *European Journal of Pain* 16(2), pp. 289–299. Available at: http://doi.wiley.com/10.1016/j.ejpain.2011.07.006.

Gyrd-Hansen, D. 2005. Willingness to pay for a QALY: theoretical and methodological issues. *PharmacoEconomics* 23(5), pp. 423–432. Available at: http://link.springer.com/10.2165/00019053-200523050-00002.

Hamunen, K. et al. 2012. Trends in opioid consumption in the Nordic countries 2002-2006. *European Journal of Pain* 13(9), pp. 954–962. Available at: http://doi.wiley.com/10.1016/j.ejpain.2008.11.006.

Hanna, L. et al. 2020. "My life is under control with these medications": an interpretative phenomenological analysis of managing chronic pain with opioids. *BMC Musculoskeletal Disorders* 21(1), p. 61. Available at: https://doi.org/10.1186/s12891-020-3055-5.

Hanna, M. 2012. Pain in Europe: A Public Health Priority. *Journal of pain & palliative care pharmacotherapy* 26(2), pp. 182-184 3p. Available at: http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=104471393&site=ehost-live&scope=site&authtype=shib&custid=s8000044.

Hansen, A.B. et al. 2015. Consumption of and satisfaction with healthcare among opioid users with chronic non-malignant pain. *Acta anaesthesiologica Scandinavica* 59(10), pp. 1355–1366. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26113028&retmode=ref&cmd=prlinks.

Härdle, W. et al. 1997. A Review of Nonparametric Time Series Analysis. *International Statistical Review* 65(1), pp. 49–72. Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1751-5823.1997.tb00367.x.

Harrison, H. 2018. *Personal Communication.* Discussion about quality prescribing guidelines.

Harrison, H. and Cormack, J. 2018. Quality Prescribing for Chronic Pain: A guide for improvement 2018-2021. Available at: https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/03/Strategy-Chronic-Pain-Quality-Prescribing-for-Chronic-Pain-2018.pdf [Accessed: 4 June 2019].

Hart, J.T. 1971. The health of coal mining communities. *Journal of the Royal College of General Practitioners* 21, pp. 517–528.

Häuser, W. et al. 2021. European* clinical practice recommendations on opioids for chronic noncancer pain – Part 1: Role of opioids in the management of chronic noncancer pain. *European Journal of Pain* 25(5), pp. 949–968. doi: 10.1002/ejp.1736.

Hawkes, N. 2013. Deaths from tramadol and legal highs reach new highs in England and Wales. *BMJ* 347(aug30 2), pp. f5336–f5336. Available at: http://www.bmj.com/cgi/doi/10.1136/bmj.f5336.

Hayhurst, C.J. et al. 2018. Pain and Its Long-term Interference of Daily Life After Critical Illness. *Anesthesia and analgesia* 127(3), pp. 690–697. Available at: https://journals.lww.com/anesthesia-analgesia/Fulltext/2018/09000/Pain_and_Its_Long_term_Interference_of_Daily_Life.19.aspx.

Healthcare Improvement Scotland 2014. *Chronic Pain Services in Scotland: Where are we now?* Available at: https://www.healthcareimprovementscotland.org/our_work/long_term_conditions/chronic_pain/where_are_we_now.aspx [Accessed: July 9, 2021].

Hebert, H.L. et al. 2021. Assessing the impact of SIGN 136 on opioid prescribing rates in Scotland: An interrupted time series analysis. *medRxiv* , p. 2021.02.19.21251770–18. Available at: https://www.medrxiv.org/content/10.1101/2021.02.19.21251770v1.

Heins, S.E. et al. 2018. High-Risk Prescribing to Medicaid Enrolees Receiving Opioid Analgesics: Individual- and County-Level Factors. *Substance use & misuse* 53(10), pp. 1591–1601. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29303393&retmode=ref&cmd=prlinks.

Helgason, I.S. 2008. *Predicting Prescription Patterns*. Available at: https://dspace.mit.edu/bitstream/handle/1721.1/43873/263428528-MIT.pdf?sequence=2&isAllowed=y

Henriksen, G. and Willoch, F. 2008. Imaging of opioid receptors in the central nervous system. *Brain* 131, pp. 1171–1196. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2367693/.

Henschke, N. et al. 2015. The epidemiology and economic consequences of pain. *Mayo Clinic proceedings* 90(1), pp. 139–147. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25572198&retmode=ref&cmd=prlinks.

Hider-Mlynarz, K. et al. 2018. Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe. *British Journal of Clinical Pharmacology* 84, pp. 1324–1334. Available at: https://bpspubs.onlinelibrary.wiley.com/doi/pdf/10.1111/bcp.13564.

Higgins, C. et al. 2019. Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis. *British journal of anaesthesia* 122(6), pp. e114–e126. Available at: https://doi.org/10.1016/j.bja.2018.09.019.

Hilderink, P.H. et al. 2012. The Temporal Relation Between Pain and Depression: Results from the Longitudinal Aging Study Amsterdam. *Psychosomatic medicine* 74(9), pp. 945–951. Available at: https://journals.lww.com/psychosomaticmedicine/Fulltext/2012/11000/The_Temporal_Relation_Between_Pain_and_Depression_.12.aspx.

Hoffman, K.M. et al. 2016. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proceedings of the National Academy of Sciences of the United States of America* 113(16), pp. 4296–4301. doi: 10.1073/pnas.1516047113.

Holloway, K. et al. 2018. Fatal and non-fatal overdose among opiate users in South Wales: A qualitative study of peer responses. *The International journal on drug policy* 56, pp. 56–63. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29605706&retmode=ref&cmd=prlinks.

Home Office 2019. *Drugs Misuse: Findings from the 2018/19 Crime Survey for England and Wales*. Available at: https://www.gov.uk/government/statistics/drug-misuse-findings-from-the-2018-to-2019-csew [Accessed: May 14, 2021].

Hong, J. et al. 2013. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. *Spine* 38(1), pp. 75–82. Available at: https://journals.lww.com/spinejournal/Abstract/2013/01010/Costs_Associated_With_Treatment_of_Chronic_Low.13.aspx.

Hong, L. et al. 2019. Big Data in Health Care: Applications and Challenges. *Data and Information Management* 2(3), pp. 175–197. Available at: https://content.sciendo.com/doi/10.2478/dim-2018-0014.

Hoy, D. et al. 2014. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases* 73(6), pp. 968–974. Available at: http://ard.bmj.com/cgi/doi/10.1136/annrheumdis-2013-204428.

Huang, A.R. and Mallet, L. 2013. Prescribing opioids in older people. *Maturitas* 74(2), pp. 123–129. Available at: http://dx.doi.org/10.1016/j.maturitas.2012.11.002.

Hughes, O. 2018. Researchers say analysis of prescribing hampered by "poor quality" NHS data. Available at: https://www.digitalhealth.net/2018/08/researchers-say-prescribing-analysis-hampered-poor-quality-data/ [Accessed: 6 May 2021].

Hull, S. et al. 1998. The use and overlap of AED and general practice services by patients registered at two inner London general practices. *British Journal of General Practice* 46, pp. 1575–1579.

Hunt, K.A. et al. 2006. Characteristics of Frequent Users of Emergency Departments. *Annals of emergency medicine* 48(1), pp. 1–8. doi: 10.1016/j.annemergmed.2005.12.030.

Husain, M.J. et al. 2013. Linked routine data to enhance health-economics analysis. *Farmeconomia. Health economics and therapeutic pathways* 14(2), pp. 47–49. Available at: http://test-journals-3.1.2.seedmedicalpublishers.com/index.php/FE/article/view/677/769.

Husky, M.M. et al. 2018. Chronic back pain and its association with quality of life in a large French population survey. *Health and Quality of Life Outcomes* 16(1), pp. 1–9. doi: 10.1186/s12955-018-1018-4.

IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

Ikenberg, R. et al. 2012. Cost-effectiveness of tapentadol prolonged release compared with oxycodone controlled release in the UK in patients with severe non-malignant chronic pain who failed 1st line treatment with morphine. *Journal of Medical Economics* 15(4), pp. 724–736. Available at: https://doi.org/10.3111/13696998.2012.670174.

Information Commissioner 2021. Information Commissioners Office. Available at: ico.org.uk [Accessed: 6 February 2021].

Institute for Health Metrics and Evaluation. Available at: http://www.healthdata.org [Accessed: 3 April 2021].

International Association for the Study of Pain (IASP) 2019. Chronic Pain has arrived in the ICD-11. Available at: https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=8340

International Narcotics Control Board 2016. *Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purposes*. Vienna: United Nations. Available at: https://www.unodc.org/documents/drug-prevention-and-treatment/INCB_Access_Supplement-AR15_availability_English.pdf.

IQVIA 2020. Prescription opioid use in the US has declined by 60% from 2011 peak, according to new report from the IQVUA Institute for human data science. Available at:

https://www.iqvia.com/newsroom/2020/12/prescription-opioid-use-in-the-us-has-declined-by-60-from-2011-peak-according-to-new-report-from-the [Accessed: 9 April 2021].

Iroju, O.G. and Olaleke, J.O. 2015. A Systematic Review of Natural Language Processing in Healthcare. *International Journal of Information Technology and Computer Science* 7(8), pp. 44–50. Available at: http://www.mecs-press.org/ijitcs/ijitcs-v7-n8/v7n8-7.html.

Islam, M. M., & Wollersheim, D. (2019). A comparison of opioids and benzodiazepines dispensing in Australia. *PloS One*, *14*(8), e0221438-13. https://doi.org/10.1371/journal.pone.0221438

Jain, N. et al. 2018. Chronic preoperative opioid use is a risk factor for increased complications, resource use, and costs after cervical fusion. *The spine journal : official journal of the North American Spine Society* 18(11), pp. 1989–1998. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1529943018301268.

Janevic, M.R. et al. 2017. Racial and Socioeconomic Disparities in Disabling Chronic Pain: Findings from the Health and Retirement Study. *The Journal of Pain* 18(12), pp. 1459–1467. doi: 10.1016/j.jpain.2017.07.005.

Jani, M. et al. 2020. Time trends and prescribing patterns of opioid drugs in UK primary care patients with non-cancer pain: A retrospective cohort study. *PLoS Medicine* 17(10), pp. e1003270-16. doi: 10.1371/journal.pmed.1003270. doi: 10.1101/2020.04.07.20049015.

Jarlbaek, L. et al. 2005. Use of Opioids in a Danish Population-Based Cohort of Cancer Patients. *Journal of Pain and Symptom Management* 29(4), pp. 336–343. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0885392405000540.

Jee, K. and Kim, G.-H. 2013. Potentiality of Big Data in the Medical Sector: Focus on How to Reshape the Healthcare System. *Healthcare Informatics Research* 19(2), pp. 79–8. Available at: http://e-hir.org/journal/view.php?id=10.4258/hir.2013.19.2.79.

Jennings, P.A. et al. 2009. Measuring acute pain in the prehospital setting. *Emergency medicine journal : EMJ* 26(8), pp. 552–555. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19625547&retmode=ref&cmd=prlinks.

Jensen, M.K. et al. 2006. 10-year follow-up of chronic non-malignant pain patients: Opioid use, health related quality of life and health care utilization. *European Journal of Pain* 10(5), pp. 423–433. Available at: https://www.sciencedirect.com/science/article/pii/S109038010500073X.

Jesulola, E. et al. 2018. Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model - are we there yet? *Behavioural Brain Research* 341, pp. 79–90. Available at: https://www.sciencedirect.com/science/article/pii/S0166432817318521?via%3Dihub.

Jimenez, N. et al. 2011. A review of the experience, epidemiology, and management of pain among American Indian, Alaska Native, and Aboriginal Canadian peoples. *The Journal of Pain* 12(5), pp. 511–522. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21330217&retmode=ref&cmd=prlinks.

Johnson, Q. et al. 2013. A Review of Management of Acute Pain. *MIssouri Medicine* 110(1), pp. 74–79.

Johnston, D.A. et al. 2019. The relationship between depression symptoms, absenteeism and presenteeism. *Journal of Affective Disorders* 256, pp. 536–540. Available at: https://www.sciencedirect.com/science/article/pii/S016503271930028X.

Joint Formulary Committee. 2021. BNF: British National Formulary - NICE. Available at: https://bnf.nice.org.uk/guidance/controlled-drugs-and-drug-dependence.html.

Jones, C.A. et al. 2009. *Health status and health care access of farm and rural populations*. Available at: https://www.ers.usda.gov/webdocs/publications/44424/9371_eib57_1_.pdf.

Jones, K.F. et al. 2020. Exploring factors associated with long-term opioid therapy in cancer survivors: an integrative review. *Journal of Pain and Symptom Management* . doi: 10.1016/j.jpainsymman.2020.08.015.

Jones, K.H. et al. 2014. A case study of the Secure Anonymous Information Linkage (SAIL) Gateway: A privacy-protecting remote access system for health-related research and evaluation. *Journal of Biomedical Informatics* 50, pp. 196–204. Available at: http://linkinghub.elsevier.com/retrieve/pii/S1532046414000045.

Joseph Rowntree Foundation 2013. Monitoring poverty and social exclusion 2013. Available at: https://www.jrf.org.uk/report/monitoring-poverty-and-social-exclusion-2013 [Accessed: 5 March 2020].

Joynt, M. et al. 2013. The Impact of Neighborhood Socioeconomic Status and Race on the Prescribing of Opioids in Emergency Departments Throughout the United States. *Journal of General Internal Medicine* 28(12), pp. 1604–1610. doi: 10.1007/s11606-013-2516-z.

Justins, D.M. 1996. Management strategies for chronic pain. *Annals of the Rheumatic Diseases* 55(9), p. 588. Available at: https://ard.bmj.com/content/annrheumdis/55/9/588.full.pdf.

Kaplow, L. and Shavell, S. 2001. kaplow-shavell_(jpe01).pdf. *The Journal of Political Economy* 109(2), pp. 281–286. Available at: http://links.jstor.org/sici?sici=0022-3808%28200104%29109%3A2%3C281%3AANMOPA%3E2.0.CO%3B2-R.

Kapoor, S. and Thorn, B.E. 2014; *Healthcare use and prescription of opioids in rural residents with pain*. Rural and Remote Health. 14: 2879. https://doi.org/10.22605/RRH2879

Karanges, E.A. et al. 2016. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. *British Journal of Clinical Pharmacology* 82(1), pp. 255–267. doi: 10.1111/bcp.12937.

Katz, J.N. et al. 2016. Cost-effectiveness of nonsteroidal anti-inflammatory drugs and opioids in the treatment of knee osteoarthritis in older patients with multiple comorbidities. *Osteoarthritis and Cartilage* 24(3), pp. 409–418. doi: 10.1016/j.joca.2015.10.006.

Katz, N. and Mazer, N.A. 2009. The impact of opioids on the endocrine system. *The Clinical journal of pain* 25(2), pp. 170–175. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=19333165&retmode=ref&cmd=prlinks.

Kaufman, A.R. and Hersh, E.D. 2020. The political consequences of opioid overdoses. *PloS one* 15(8), p. e0236815. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=32750079&retmode=ref&cmd=prlinks.

Kawulich, B. 2012. Selecting a research approach: paradigm, methodology and methods. In: *Doing social research: A global context*. McGraw-Hill Higher Education, pp. 51–61. Available at: https://www.researchgate.net/profile/Barbara-Kawulich/publication/257944787_Selecting_a_research_approach_Paradigm_methodology_and_methods/links/56166fc308ae37cfe40910fc/Selecting-a-research-approach-Paradigm-methodology-and-methods.pdf [Accessed: 16 February 2021].

Kay, C. et al. 2017. Utilization of Healthcare Services and Ambulatory Resources Associated with Chronic Noncancer Pain. *Pain Medicine* 18(7), pp. 1236–1246. Available at: https://academic.oup.com/painmedicine/article-lookup/doi/10.1093/pm/pnw336.

Keefe, F.J. et al. 2000. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain* 87(3), pp. 325–334. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006396-200008020-00010.

Kenan, K. et al. 2012. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000–2010. *Open Medicine* 6(2), pp. 41-47–2547. doi: 10.2105/ajph.2009.180646.

Kern, D.M. et al. 2015. Treatment patterns, healthcare utilization, and costs of chronic opioid treatment for non-cancer pain in the United States. *The American Journal of Managed Care* 21(3), pp. e222-34. Available at: https://www.ajmc.com/view/treatment-patterns-healthcare-utilization-and-costs-of-chronic-opioid-treatment-for-non-cancer-pain-in-the-united-states.

Keyes, K.M. et al. 2014. Understanding the rural-urban differences in nonmedical prescription opioid use and abuse in the United States. *American Journal of Public Health* 104(2), pp. e52-9. Available at: http://ajph.aphapublications.org/doi/10.2105/AJPH.2013.301709.

Khaldi, K. 2017. Quantitative, Qualitative or Mixed Research: Which Research Paradigm to Use? *Journal of Educational and Social Research* 7(2), pp. 15–24. doi: 10.5901/jesr.2017.v7n2p15.

Kinnaird, E. et al. 2019. From pain treatment to opioid dependence: a qualitative study of the environmental influence on codeine use in UK adults. *BMJ open* 9(4), pp. e025331-10. Available at: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2018-025331.

Kluwer, W. 2021. Morphine Equivalent Dosing. Available at: https://www.wolterskluwercdi.com/sites/default/files/documents/ebooks/morphine-equivalent-dosing-ebook.pdf?v3 [Accessed: 5 September 2021].

Knights, D. et al. 2018. 'Please make comfortable': prescribing opioids in the wake of Gosport. *British Journal of General Practice* 68(675), pp. 462–463. Available at: https://bjgp.org/content/68/675/462.

Kolodny, A. and Frieden, T.R. 2017. Ten Steps the Federal Government Should Take Now to Reverse the Opioid Addiction Epidemic. *JAMA* 318(16), pp. 1537–1538. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29049522&retmode=ref&cmd=prlinks.

Korff, M.V. et al. 2008. De Facto Long-term Opioid Therapy for Noncancer Pain. *The Clinical Journal of Pain* 24(6), pp. 521–527. doi: 10.1097/ajp.0b013e318169d03b.

Kotecha, M.K. and Sites, B.D. 2013. Pain policy and abuse of prescription opioids in the USA: a cautionary tale for Europe. *Anaesthesia* 68(12), pp. 1210–1215. Available at: http://doi.wiley.com/10.1111/anae.12450.

Krebs, E.E. et al. 2018. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *JAMA* 319(9), pp. 872–882. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29509867&retmode=ref&cmd=prlinks.

Kruse, C.S. et al. 2016. Challenges and Opportunities of Big Data in Health Care: A Systematic Review. *JMIR medical informatics* 4(4), p. e38. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27872036&retmode=ref&cmd=prlinks.

Kurani, S. et al. 2020. Place, poverty and prescriptions: a cross-sectional study using Area Deprivation Index to assess opioid use and drug-poisoning mortality in the USA from 2012 to 2017. *BMJ open* 10(5), pp. e035376-7. doi: 10.1136/bmjopen-2019-035376.

Lachance, C. and Frey, N. 2019. *Prescription Monitoring Programs for Optimizing Medication Use and Preventing Harm*. Available at: http://books.google.co.uk/books?id=q85dzQEACAAJ&dq=prescription+monitoring&hl=&cd=3&source=gbs_api.

Lalic, S. et al. 2018. Predictors of persistent prescription opioid analgesic use among people without cancer in Australia. *British Journal of Clinical Pharmacology* 84(6), pp. 1267–1278. doi: 10.1111/bcp.13556.

Lambeek, L.C. et al. 2011. The trend in total cost of back pain in The Netherlands in the period 2002 to 2007. *Spine* 36(13), pp. 1050–1058. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21150697&retmode=ref&cmd=prlinks.

Laney, D. (2001) 3D Data Management: Controlling Data Volume, Velocity and Variety. META Group Research Note, 6. Available at: http://blogs.gartner.com/doug-laney/files/2012/01/ad949-3D-Data-Management-Controlling-Data-Volume-Velocity-and-Variety.pdf

Lange, L.L. and Jacox, A. 1993. Using large data bases in nursing and health policy research. *Journal of professional nursing : official journal of the American Association of Colleges of Nursing* 9(4), pp. 204–211. Available at: https://linkinghub.elsevier.com/retrieve/pii/875572239390037D.

Large, R.G. and Schug, S.A. 1995. Opioids for chronic pain of non-malignant origin—Caring or crippling. *Healthcare Analysis* 3(1), p. 5. Available at: https://doi.org/10.1007/BF02197187.

Larney, S. et al. 2018. Using routinely collected data to understand and predict adverse outcomes in opioid agonist treatment: Protocol for the Opioid Agonist Treatment Safety (OATS) Study. *BMJ open* 8(8), pp. e025204-6. Available at: http://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2018-025204.

Latham, J. and Davis, B.D. 1994. The socioeconomic impact of chronic pain. *Disability and rehabilitation* 16(1), pp. 39–44. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=8136509&retmode=ref&cmd=prlinks.

Lautenbacher, S. et al. 2017. Age changes in pain perception: A systematic-review and meta-analysis of age effects on pain and tolerance thresholds. *Neuroscience and biobehavioral reviews* 75, pp. 104–113. Available at: http://dx.doi.org/10.1016/j.neubiorev.2017.01.039.

Lavrakas, P. 2008. Encyclopedia of Survey Research Methods. doi: 10.4135/9781412963947.

Lawton, S. and Miles, G. 2019. Occupational skin and lung disease in coalfield communities. *Nursing Times* 115(7), pp. 58–60. Available at: https://insights.ovid.com/nursing-times/nrtm/2019/07/000/occupational-skin-lung-disease-coalfield/44/00006203.

Lee, M. et al. 2011. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 14, pp. 145–161. Available at: https://www.painphysicianjournal.com/current/pdf?article=MTQ0Ng%3D%3D&journal=60.

legislation.gov.uk and UK Government 2021. Misuse of Drugs Regulations 2001. Available at: https://www.legislation.gov.uk/uksi/2001/3998/schedule/1/made [Accessed: 5 September 2021].

LeResche, L. et al. 2005. Relationship of pain and symptoms to pubertal development in adolescents. *Pain* 118(1–2), pp. 201–209. doi: 10.1016/j.pain.2005.08.011.

Levy, B. et al. 2015. Trends in Opioid Analgesic–Prescribing Rates by Specialty, U.S., 2007–2012. *American Journal of Preventive Medicine* 49(3), pp. 409–413. doi: 10.1016/j.amepre.2015.02.020.

Levy, N. et al. 2021. An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=33027841&retmode=ref&cmd=prlinks [Accessed: 1 June 2021].

Lewer, D. et al. 2020. Frequency of health-care utilization by adults who use illicit drugs: a systematic review and meta-analysis. *Addiction (Abingdon, England)* 115(6), pp. 1011–1023. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=31705770&retmode=ref&cmd=prlinks.

Liberman, J.S. et al. 2019. Opioid prescriptions at hospital discharge are associated with more post discharge healthcare utilization. *Am Heart Assoc* 8(3), p. e010664. Available at: https://www.ahajournals.org/doi/abs/10.1161/jaha.118.010664.

Liddell, D. 2019. Poverty is the root cause of Scotland's fatal drug overdose crisis. Available at: https://www.povertyalliance.org/blog-poverty-is-the-root-of-scotlands-fatal-drug-overdose-crisis/.

Lin, D.H. et al. 2017. Financial Conflicts of Interest and the Centers for Disease Control and Prevention's 2016 Guideline for Prescribing Opioids for Chronic Pain. *JAMA Internal Medicine* 177(3), p. 427. doi: 10.1001/jamainternmed.2016.8471.

Loudon, I. 2008. The principle of referral: the gatekeeping role of the GP. *The British journal of general practice : the journal of the Royal College of General Practitioners* 58(547), pp. 128–30--discussion 130. Available at: https://bjgp.org/content/58/547/128.abstract.

Loyland, B. 2016. The co-occurrence of chronic pain and psychological distress and its associations with salient socio-demographic characteristics among long-term social assistance

recipients in Norway. *Scandinavian Journal of Pain* 11(1), pp. 65–72. Available at: https://www.degruyter.com/view/journals/sjpain/11/1/article-p65.xml.

Lozano-Ondoua, A. et al. 2013. Mechanisms of cancer-induced bone pain. *Neuroscience Letters* 0 0(557), pp. 52–59. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542064/pdf/nihms527830.pdf.

Lumley, T. et al. 2002. The importance of the normality assumption in large public health data sets. *Annual review of public health* 23(1), pp. 151–169. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=11910059&retmode=ref&cmd=prlinks.

Lusa, S. et al. 2015. Sleep disturbances predict long-term changes in low back pain among Finnish firefighters: 13-year follow-up study. *International Archives of Occupational and Environmental Health* 88(3), pp. 369–379. Available at: https://doi.org/10.1007/s00420-014-0968-z.

Lutz, P.-E. and Kieffer, B.L. 2013. The multiple facets of opioid receptor function: implications for addiction. *Current Opinion in Neurobiology* 23(4), pp. 473–479. doi: https://doi.org/10.1016/j.conb.2013.02.005.

Lynch, M.E. et al. 2008. A systematic review of the effect of waiting for treatment for chronic pain. *Pain* 136(1–2), pp. 97–116. Available at: https://journals.lww.com/pain/Fulltext/2008/05000/A_systematic_review_of_the_effect_of_waiting_for.14.aspx.

Lyons, R.A. et al. 2009. The SAIL databank: linking multiple health and social care datasets. *BMC Medical Informatics and Decision Making* 9(1), p. 3. Available at: http://bmcmedinformdecismak.biomedcentral.com/articles/10.1186/1472-6947-9-3.

Ma, C. et al. 2015. Big data in pharmacy practice: current use, challenges, and the future. *Integrated Pharmacy Research and Practice* Volume 4, pp. 91–9. Available at: http://www.dovepress.com/big-data-in-pharmacy-practice-current-use-challenges-and-the-future-peer-reviewed-article-IPRP.

Macfarlane, G.J. et al. 2009. The influence of socioeconomic status on the reporting of regional and widespread musculoskeletal pain: results from the 1958 British Birth Cohort Study. *Annals of the Rheumatic Diseases* 68(10), pp. 1591–1595. doi: 10.1136/ard.2008.093088.

Macfarlane, G.J. et al. 2020. The epidemiology of regular opioid use and its association with mortality: Prospective cohort study of 466 486 UK biobank participants., pp. 1–8. doi: 10.1016/j.eclinm.2020.100321.

Mackes, N.K. et al. 2020. Early childhood deprivation is associated with alterations in adult brain structure despite subsequent environmental enrichment. ["Sonuga-Barke et al. eds. *Proceedings of the National Academy of Sciences* 117(1), pp. 641–649. Available at: https://www.pnas.org/content/117/1/641.

Mackey, M.-C.K.S. 2019. Managing twin crises in chronic pain and prescription opioids. *BMJ* 364, pp. 1–2. Available at: http://dx.doi.org/doi:10.1136/bmj.l917.

MacQueen, I.T. et al. 2018. Recruiting rural healthcare providers today: a systematic review of training program success and determinants of geographic choices. *Journal of General and Internal Medicine* 33(2), pp. 191–199. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5789104/pdf/11606_2017_Article_4210.pdf.

Maniadakis, N. and Gray, A. 2000. The economic burden of back pain in the UK. *Pain* 84(1), pp. 95–103. Available at: http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=104718901&site=ehost-live&scope=site&authtype=shib&custid=s8000044.

Mann, E.G., et al. 2016. Frequency and characteristics of healthcare visits associated with chronic pain: results from a population-based Canadian study. *Canadian Journal of Anesthesiology* 63, pp. 411–441. Available at: https://link.springer.com/content/pdf/10.1007/s12630-015-0578-6.pdf.

Marks, J.H. 2020. Lessons from Corporate Influence in the Opioid Epidemic: Toward a Norm of Separation. *Journal of Bioethical Inquiry* 17(2), pp. 1–17. doi: 10.1007/s11673-020-09982-x.

Marmot, M. 2005. Social determinants of health inequalities. *The Lancet* 365(9464), pp. 1099–1104. Available at: https://www.sciencedirect.com/science/article/pii/S0140673605711466.

Marmot, M. 2017. Closing the health gap. *Scandinavian journal of public health* 45(7), pp. 723–731. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29162013&retmode=ref&cmd=prlinks.

Marmot, M. and Bell, R. 2012. Fair society, healthy lives. *Public Health* 126, pp. S4–S10. Available at: https://www.sciencedirect.com/science/article/pii/S0033350612001862.

Marouf, R. et al. 2014. Reduced pain inhibition is associated with reduced cognitive inhibition in healthy aging. *Pain* 155(3), pp. 494–502. Available at: http://dx.doi.org/10.1016/j.pain.2013.11.011.

Marsh, S. 2017. “Unnecessary” painkillers could leave thousands addicted, doctors warn. *The Guardian* . Available at: http://www.theguardian.com/science/2017/may/05/unnecessary-opioid-painkiller-prescriptions-thousands-addicted-nhs-doctors-warn.

Marsh, S. 2021. “I was told to live with it”: women tell of doctors dismissing their pain. *The Guardian* 16 April. Available at: https://www.theguardian.com/society/2021/apr/16/painkillers-women-tell-of-doctors-dismissing-their-pain.

Martin, J. et al. 2018. Effect of restricting the legal supply of prescription opioids on buying through online illicit marketplaces: Interrupted time series analysis. *BMJ* 361, p. k2270. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=29899119&retmode=ref&cmd=prlinks.

Martinez, C. 2018. Cracking the Code: Using Data to Combat the Opioid Crisis. *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine \& Ethics* 46(2), pp. 454–471. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30146995&retmode=ref&cmd=prlinks.

Matthias, M.S. 2020. Opioid Tapering and the Patient-Provider Relationship. *Journal of General Internal Medicine* 35(1), pp. 8–9. doi: 10.1007/s11606-019-05337-4.

Matthias, M.S. et al. 2013. “I’m not abusing or anything”: patient-physician communication about opioid treatment in chronic pain. *Patient Education and Counseling* 93(2), pp. 197–202. doi: 10.1016/j.pec.2013.06.021.

Matthias, M.S. et al. 2014. Communicating about opioids for chronic pain: a qualitative study of patient attributions and the influence of the patient-physician relationship. *European Journal of Pain* 18(6), pp. 835–843. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/j.1532-2149.2013.00426.x.

Mauro, A.D. et al. 2016. A formal definition of Big Data based on its essential features. *Library Review* 65(3), pp. 122–135. Available at: https://www.emerald.com/insight/content/doi/10.1108/LR-06-2015-0061/full/html.

Mazereeuw, G. et al. 2018. Depression in chronic pain: might opioids be responsible? *Pain* 159(11), pp. 2142–2145. doi: 10.1097/j.pain<.0010000000001305.

Mazure, C.M. and Fiellin, D.A. 2018. Women and opioids: something different is happening here. *The Lancet* 392(10141), pp. 9–11. Available at: http://dx.doi.org/10.1016/S0140-6736(18)31203-0.

McAreavey, R. and Brown, D.L. 2019. Comparative analysis of rural poverty and inequality in the UK and the US. *Palgrave Communications* 5(1), pp. 1–10. Available at: http://dx.doi.org/10.1057/s41599-019-0332-8.

McCormick, B. et al. 2012. *Are hospital services used differently in deprived areas? Evidence to identify commissioning challenges. Working Paper No 2*. Oxford: Centre for Health Service Economics and Organisation~. Available at: https://www.chseo.org.uk/downloads/wp2-hospitalservices-deprivedareas.pdf.

McCrorie, C. et al. 2015. Understanding long-term opioid prescribing for non-cancer pain in primary care: a qualitative study. *BMC Family Practice* 16(1), pp. 1–9. Available at: http://dx.doi.org/10.1186/s12875-015-0335-5.

McEwen, J. 2004. *Chronic Pain Services in Scotland: Report by Professor James McEwen*. Edinburgh: Scottish Executive Health Department., pp. 1–25. Available at: https://www.sehd.scot.nhs.uk/mels/hdl2004_48.pdf.

McGorm, K. et al. 2010. Patients repeatedly referred to secondary care with symptoms unexplained by organic disease: prevalence, characteristics and referral pattern. *Family practice* 27(5), pp. 479–486. doi: 10.1093/fampra/cmq053.

McGreal, C., 2018. American Overdose, The Opioid Tragedy in Three Acts. Guardian Faber Publishing, London. ISBN: 1783351683

McIntosh, T. et al. 2016. Influences on prescribing decision-making among non-medical prescribers in the United Kingdom: systematic review. *Family practice* 33(6), pp. 572–579. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27543795&retmode=ref&cmd=prlinks.

McLaughlin, K.A. et al. 2014. Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. *Neuroscience & Biobehavioral Reviews* 47, pp. 578–591. doi: 10.1016/j.neubiorev.2014.10.012.

McMillan, M. et al. 2015. Prevalence of Musculoskeletal Disorders Among Saskatchewan Farmers. *Journal of Agromedicine* 20(3), pp. 292–301. Available at: https://doi.org/10.1080/1059924X.2015.1042611.

Medicines and Healthcare products Regulatory Agency 2021. Yellow Card. Available at: https://www.gov.uk/report-problem-medicine-medical-device [Accessed: 15 June 2021].

Mehra, M. et al. 2011. The burden of chronic low back pain with and without a neuropathic component: a healthcare resource use and cost analysis. *Journal of Medical Economics* 15(2), pp. 245–252. doi: 10.3111/13696998.2011.642090.

Mehta, N. and Pandit, A. 2018. Concurrence of big data analytics and healthcare: A systematic review. *International journal of medical informatics* 114(1), pp. 57–65. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1386505618302466.

Meints, S.M. and Edwards, R.R. 2018. Evaluating psychosocial contributions to chronic pain outcomes. *Progress in Neuropsychopharmacology & Biological Psychiatry* 87(Part B), pp. 168–182. Available at: https://doi.org/10.1016/j.pnpbp.2018.01.017.

Meldrum, M.L. 2003. A capsule history of pain management. *JAMA* 290(18), pp. 2470–5. Available at: https://pubmed.ncbi.nlm.nih.gov/14612484/.

Mellor, R. and Chronic Pain Policy Group 2018. *Scottish Public Health Network (ScotPHN) report: Health Care Needs Assessment of Adult Chronic Pain Services in Scotland*. Glasgow: Scottish Public Health Network. Available at: www.scotphn.net.

Melzack, R. and Wall, P.D. 1965. Pain mechanisms: a new theory. *Science* 150(3699), pp. 971–979. Available at: http://scholar.google.com/scholar?q=related:pYHDAy030AAJ:scholar.google.com/&hl=en&num=20&as_sdt=0,5.

Menchetti, M. et al. 2009. Recognition and treatment of depression in primary care: effect of patients' presentation and frequency of consultation. 66(4), pp. 335–341. doi: 10.1016/j.jpsychores.2008.10.008.

Mercadante, S. et al. 2019. Opioid-Induced Tolerance and Hyperalgesia. *CNS Drugs* 33(10), pp. 943–955. doi: 10.1007/s40263-019-00660-0.

Merrill, T. and Kitson, L. 2017. *End of Coal Mining in South Wales: Lessons learned from industrial transformation*. Geneva: International Institute for Sustainable Development. Available at: https://www.iisd.org/system/files/publications/end-of-coal-mining-south-wales-lessons-learned.pdf.

Merriwether, E.N. et al. 2018. Physical activity is related to function and fatigue but not pain in women with fibromyalgia: baseline analyses from the Fibromyalgia Activity Study with TENS (FAST). *Arthritis research & therapy* 20(1), pp. 199–13. Available at: https://arthritis-research.biomedcentral.com/articles/10.1186/s13075-018-1671-3.

Meyer, A. et al. 2020. Prescription Opioid Prescribing in Western Europe and the United States. *Rhode Island medical journal (2013)* 103(2), pp. 45–48. Available at: http://www.rimed.org/rimedicaljournal/2020/03/2020-03-45-contribution-meyer.pdf.

Michael, P.F. 2008. Public Health in Wales (1800-2000): A brief history. Available at: http://scholar.google.comjavascript:void(0).

Microsoft Corporation 2018. Microsoft Excel. Available at: https://office.microsoft.com/excel [Accessed: 8 January 2021].

Mills, S. et al. 2016. Identification and Management of Chronic Pain in Primary Care: a Review. *Current Psychiatry Reports* 18(2), pp. 1–9. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26820898&retmode=ref&cmd=prlinks.

Ministry of Housing 2019. English indices of deprivation 2019. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019 [Accessed: 7 September 2018].

Mogil, J.S. and Chanda, M.L. 2005. The case for the inclusion of female subjects in basic science studies of pain. *Pain* 117(1–2), pp. 1–5. doi: 10.1016/j.pain.2005.06.020.

Molton, I.R. and Terrill, A.L. 2014. Overview of persistent pain in older adults. *American Psychologist* 69(2), pp. 197–207. Available at: http://doi.apa.org/getdoi.cfm?doi=10.1037/a0035794.

Moore, F.R. et al. 2020. Sociodemographic predictors of attendance at a Scottish pain management programme. *British Journal of Pain* , pp. 1–8. Available at: https://doi.org/10.1177/2049463720970579.

Moore, L. et al. 2009. Characteristics of frequent attenders in an emergency department: analysis of 1-year attendance data. *Emergency medicine journal : EMJ* 26(4), pp. 263–267. doi: 10.1136/emj.2008.059428.

Mordecai, L. et al. 2018. Patterns of regional variation of opioid prescribing in primary care in England: a retrospective observational study. *The British journal of general practice : the journal of the Royal College of General Practitioners* 68(668), pp. e225–e233. doi: 10.3399/bjgp18x695057. Available at: https://bjgp.org/content/68/668/e225.abstract.

Morgan, C.L. et al. 2011. The relationship between self-reported severe pain and measures of socio-economic disadvantage. *European journal of pain (London, England)* 15(10), pp. 1107–1111. doi: 10.1016/j.ejpain.2011.04.010.

Morley, K.I. et al. 2017. Polysubstance use and misuse or abuse of prescription opioid analgesics: a multi-level analysis of international data. *Pain* 158(6), pp. 1138–1144. Available at: http://Insights.ovid.com/crossref?an=00006396-201706000-00020.

Morriss, R. et al. 2012. Persistent frequent attenders in primary care: costs, reasons for attendance, organisation of care and potential for cognitive behavioural therapeutic intervention. *BMC Family Practice* 13(1), pp. 39–14. doi: 10.1186/1471-2296-13-39.

Moseley, G.L. 2007. Reconceptualising pain according to modern pain science. *Physical Therapy Reviews* 12(3), pp. 169–178. Available at: https://doi.org/10.1179/108331907X223010.

Moseley, L.G. and Vlaeyen, J.W. 2015. Beyond nociception: the imprecision hypothesis of chronic pain. *Pain* 156(1), pp. 35–38. Available at: https://journals.lww.com/pain/Citation/2015/01000/Beyond_nociception__the_imprecision_hypothesis_of.7.aspx.

Mulvihill, G. et al. 2016. Drugmakers fight state opioid limits amid crisis. *Kitsap Sun* 18 September, p. 7A. Available at: http://web.kitsapsun.com/webdot/PDFArchive/0918A007BCKS1.PDF.

Mundkur, M.L. et al. 2017. Will strict limits on opioid prescription duration prevent addiction? Advocating for evidence-based policymaking. *Substance Abuse* 38(3), pp. 237–238. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=28632485&retmode=ref&cmd=prlinks.

Mundkur, M.L. et al. 2018. Patterns of opioid initiation at first visits for pain in United States primary care settings. *Pharmacoepidemiology and Drug Safety* 27(5), pp. 495–503. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=28971545&retmode=ref&cmd=prlinks.

Murshid, M.A. and Mohaidin, Z. 2017. Models and theories of prescribing decisions: A review and suggested a new model. *Pharmacy practice* 15(2), p. 990. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=28690701&retmode=ref&cmd=prlinks.

Musazzi, U.M. et al. 2018. Do laws impact opioids consumption? A breakpoint analysis based on Italian sales data. *Journal of pain research* 11, pp. 1665–1672. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30214276&retmode=ref&cmd=prlinks.

National Assembly Government 2010. Helping to improve Wales' health: free prescriptions three years on. Available at: http://www.wales.nhs.uk/documents/prescriptions-report-three-years.pdf.

National Audit of Cardiac Rehabilitation. 2021. Available at: https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-audit-of-cardiac-rehabilitation [Accessed: 9 February 2021].

National Collaborating Centre for Chronic Conditions 2008. Osteoarthritis: National clinical guidelines for care and management in adults. Available at: https://books.google.co.uk/books?hl=en&lr=&id=aBD4O4raN2UC&oi=fnd&pg=PR5&dq=NICE+osteoarthritis+2008&ots=L-FP35d7SJ&sig=FCPG0Johk7O7WcHnsT7guP6VohU#v=onepage&q=NICE%20osteoarthritis%202008&f=false [Accessed: 5 February 2021].

National Institute for Health and Care Excellence (NICE) 2021. *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (NG193)*. Available at: www.nice.org.uk/guidance/ng193.

National Institute for Health and Care Excellence 2016. Controlled drugs: safe use and management. Available at: https://www.nice.org.uk/guidance/ng46/evidence/full-guideline-pdf-2427186353.
National Institute for Health and Care Excellence 2016. Low back pain and sciatica in over 16s: assessment and management. Available at: www.nice.org.uk/guidance/ng59.

National Institute for Health and Care Excellence 2021. *Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain (NG193)*. Available at: www.nice.org.uk/guidance/ng193.

National Joint Registry. 2021. Available at: www.njrcentre.org.uk/njrcentre/default.aspx [Accessed: 10 March 2021].

National Office for Statistics 2013. *General Health in England and Wales: 2011 and comparison with 2001*. UK Government. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbei

ng/articles/generalhealthinenglandandwales/2013-01-30#general-health-across-the-english-regions-and-wales.

National Office for Statistics 2019 *Deaths related to drug poisoning in England and Wales: 2018 registrations*. Office for National Statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2018registrations.

National Office for Statistics 2020. Deaths related to drug poisoning in England and Wales: 2019 registrations. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2019registrations [Accessed: 2 August 2021].

National Office for Statistics 2021. Population estimates. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates [Accessed: March 2021].

National Records of Scotland Web Team 2019. National Records of Scotland. *National Records of Scotland* . Available at: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland.

National Science Foundation 2014. Critical Techniques and Technologies for Advancing Big Data Science & Engineering (BIGDATA) (nsf14543). Available at: https://www.nsf.gov/pubs/2014/nsf14543/nsf14543.htm [Accessed: 21 May 2021].

National Vascular Registry. 2021. Available at: https://www.vsqip.org.uk [Accessed: 10 February 2021].

Natusch, D. 2012. Equianalgesic doses of opioids - their use in clinical practice. *British Journal of Pain* 6(1), pp. 43–46. doi: 10.1177/2049463712437628.

Neal, R.D. et al. 1998. Frequency of patients' consulting in general practice and workload generated by frequent attenders: comparisons between practices. *The British journal of general practice : the journal of the Royal College of General Practitioners* 48(426), pp. 895–898.

Nelson, L.S. et al. 2015. Addressing the Opioid Epidemic. *JAMA* 314(14), pp. 1453–1454. Available at: https://jamanetwork.com/journals/jama/articlepdf/2456149/jed150093.pdf.

Newman, A.K. et al. 2017. The relationship of sociodemographic and psychological variables with chronic pain variables in a low-income population. *Pain* 158(9), pp. 1687–1696. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=28570481&retmode=ref&cmd=prlinks.

Newton, J.N. et al. 2015. Changes in health in England, with analysis by English regions and areas of deprivation, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 386(10010), pp. 2257–2274. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0140673615001956.

NHS Digital. 2015. UK Read Code. Available at: https://data.gov.uk/dataset/f262aa32-9c4e-44f1-99eb-4900deada7a4/uk-read-code [Accessed: 2 February 2017].

NHS Digital. 2021. Protecting patient data. Available at: https://digital.nhs.uk/services/national-data-opt-out/understanding-the-national-data-opt-out/protecting-patient-data [Accessed: 9 April 2021].

NHS Digital. 2021. SNOMED CT. Available at: https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct [Accessed: 7 February 2017].

NHS England Primary Care Group 2021. Network Contracted Direct Enhanced Service. Available at: https://www.england.nhs.uk/wp-content/uploads/2021/03/B0431-network-contract-des-specification-pcn-requirements-and-entitlements-21-22.pdf [Accessed: 4 August 2021].

NHS Quality Improvement Scotland 2007. Getting to GRIPS with Chronic Pain in Scotland. Available at: https://www.healthcareimprovementscotland.org/our_work/long_term_conditions/programme_resources/getting_to_grips_with_chronic.aspx [Accessed: 6 July 2021].

NHS Wales 2009. NHS in Wales: Why we are changing the structure. Available at: http://www.wales.nhs.uk/documents/nhs%20reform%20leaflet_october%202009.pdf [Accessed: 16 May 2020].

NHS Wales 2021. Health in Wales. Available at: https://www.wales.nhs.uk/statisticsanddata [Accessed: 2 September 2021].

Nicholas, M. et al. 2019. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain* 160(1), pp. 28–37. doi: 10.1097/j.pain<.0010000000001390.

Nicholas, M. et al. 2019. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain* 160(1), pp. 28–37. Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.4.aspx.

Nichols, V.P. et al. 2020. Experiences of people taking opioid medication for chronic non-malignant pain: a qualitative evidence synthesis using meta-ethnography. *BMJ open* 10(2), p. e032988. Available at: https://bmjopen.bmj.com/content/10/2/e032988.abstract.

Nielsen, S. et al. 2016. Health service utilisation by people living with chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. *Australian Health Review* 40(5), pp. 490–499. Available at: https://www.publish.csiro.au/ah/pdf/AH15047.

Nielsen, S. et al. 2017. Defined daily doses (DDD) do not accurately reflect opioid doses used in contemporary chronic pain treatment. *Pharmacoepidemiology and Drug Safety* 26(5), pp. 587–591. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=28101968&retmode=ref&cmd=prlinks.

Niesters, M. et al. 2010. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. *Pain* 151(1), pp. 61–68. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20692097&retmode=ref&cmd=prlinks.

Noble, M. et al. 2008. Long-Term Opioid Therapy for Chronic Noncancer Pain: A Systematic Review and Meta-Analysis of Efficacy and Safety. *Journal of Pain and Symptom Management* 35(2), pp. 214–228. doi: 10.1016/j.jpainsymman.2007.03.015.

Noble, M. et al. 2010. Long-term opioid management for chronic noncancer pain. *Cochrane Database of Systematic Reviews* (1), p. CD006605. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6494200/pdf/CD006605.pdf.

Norman, P. et al. 2014. The pits may be closed but adverse effects on health may still be evident: exploring the links between coal mine locations, socioeconomic deprivation and self~ldots. *researchgate.net* . Available at: https://www.researchgate.net/profile/Paul_Norman/publication/339626827_The_pits_may_be_closed_but_adverse_effects_on_health_may_still_be_evident_exploring_the_links_between_coal_mine_locations_socioeconomic_deprivation_and_self-reported_health_in_Great_Britain/links/5e5d01ea4585152ce8ff9d48/The-pits-may-be-closed-but-adverse-effects-on-health-may-still-be-evident-exploring-the-links-between-coal-mine-locations-socioeconomic-deprivation-and-self-reported-health-in-Great-Britain.pdf.

Northern Ireland Statistics Research Agency. Multiple Deprivation Measure 2017. Available at: https://www.nisra.gov.uk/statistics/deprivation/northern-ireland-multiple-deprivation-measure-2017-nimdm2017 [Accessed: November 2020].

Nowakowska, M. et al. 2020. Association of socioeconomic deprivation with opioid prescribing in primary care in England: a spatial analysis. *Journal of epidemiology and community health* 11(2), p. jech-2020--214676--9. Available at: https://jech.bmj.com/lookup/doi/10.1136/jech-2020-214676.

Nugraha, B. et al. 2019. The IASP classification of chronic pain for ICD-11: functioning properties of chronic pain. *Pain* 160(1), p. 88. Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.12.aspx.

O'Brien, M.D.C. and Wand, A.P.F. 2020. A systematic review of the evidence for the efficacy of opioids for chronic non-cancer pain in community-dwelling older adults. *Age and ageing* 49(2), pp. 175–183. doi: 10.1093/ageing/afz175.

OECD Health Division 2019. Using Routinely Collected Data to Inform Pharmaceutical Policies. Available at: https://www.oecd.org/health/health-systems/routinely-collected-data-to-inform-pharmaceutical-policies.htm [Accessed: 3 May 2021].

Office for National Statistics 2013. General Health in England and Wales: 2011 and comparison with 2001. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/articles/generalhealthinenglandandwales/2013-01-30 [Accessed: 19 July 2021].

Office for National Statistics 2021. Deaths related to drug poisoning in England and Wales: 2018 registrations. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2018registrations [Accessed: 26 August 2021].

Oliver, J. and Carlson, C. 2020. Misperceptions about the Opioid Epidemic: Exploring the Facts. *Pain management nursing : official journal of the American Society of Pain Management Nurses* 21(1), pp. 100–109. Available at: https://doi.org/10.1016/j.pmn.2019.05.004.

OpenPrescribing.net (2020) "Open Prescribing - Opioid Analgesic Data." Available at: https://openprescribing.net/bnf/040702/ [Accessed: June 2020]

Palmaro, A. and Lapeyre-Mestre, M. 2015. Trends in opioid analgesics use in Europe: a ten-year perspective. *Clinical Therapeutics* 37(8), p. e4. Available at: http://www.clinicaltherapeutics.com/article/S0149291815003288/fulltext.

Palmaro, A. and Lapeyre-Mestre, M. 2015. Trends in opioid analgesics use in Europe: a ten-year perspective. *Clinical Therapeutics* 37(8), p. e4. doi: 10.1016/j.clinthera.2015.05.021.

Patel, S. et al. 2015. Clinical characteristics of persistent frequent attenders in primary care: case–control study. *Family practice* 48, pp. cmv076-7. doi: 10.1093/fampra/cmv076.

Patient Knows Best 2014. NHS in Wales. Available at: https://patientsknowbest.com/wales/ [Accessed: 1 September 2021].

Pergolizzi, J.V. et al. 2017. The Basic Pharmacology of Opioids Informs the Opioid Discourse about Misuse and Abuse: A Review. *Pain and therapy* 6(1), pp. 1–16. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=28341939&retmode=ref&cmd=prlinks.

Perks, W. and Roberts, C. 2016. *Welsh Health Survey 2015: Health Service use results*. Cardiff: Welsh Government. Available at: https://gov.wales/welsh-health-survey.

Perrot, S. et al. 2019. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. *Pain* 160(1), pp. 77–82. Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.10.aspx.

Phillips, C.J. 2005. *Health Economics: an introduction for health professionals*. Oxford: Blackwell Publishing Ltd and BMJ Books.

Phillips, C.J. 2008. The real cost of pain management. *Anaesthesia* 56(11), pp. 1031–1033. Available at: http://doi.wiley.com/10.1111/j.1365-2044.2001.02367.x.

Phillips, C.J. and Harper, C. 2011. The economics associated with persistent pain. *Current opinion in Supportive and Palliative Care* 5(2), pp. 127–130. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21430542&retmode=ref&cmd=prlinks.

Pieretti, S. et al. 2016. Gender differences in pain and its relief. *Annali dell'Istituto Superiore di Sanita* 52(2), pp. 184–189. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27364392&retmode=ref&cmd=prlinks.

Pocock, L. et al. 2018. Now Gosport: what next? *British Journal of General Practice* 68(675), pp. 460–461. Available at: https://bjgp.org/content/68/675/460.

Portenoy, R.K. and Foley, K.M. 1986. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain* 25(2), pp. 171–186. doi: 10.1016/0304-3959(86)90091-6.

Powell, G.A. 2018. An Assessment of the Use of Routinely Recorded Data in the UK in a Randomised Controlled Trial. Available at: https://livrepository.liverpool.ac.uk/3026084/1/200161058_Apr2018.pdf.

Price, C. et al. 2012. *National Pain Audit Final Report 2010-2012*. Dr Foster. Available at: https://www.hqip.org.uk/wp-content/uploads/2018/02/EBfI8i.pdf.

Price, C. et al. 2019. The National Pain Audit for specialist pain services in England and Wales 2010-2014. *British Journal of Pain* 13(3), pp. 185–193. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=31308943&retmode=ref&cmd=prlinks.

Prunuske, J. P. et al. 2014. Opioid prescribing patterns for non-malignant chronic pain for rural versus non-rural US adults: a population-based study using 2010 NAMCS data. *BMC health services research*, *14*, 563. https://doi.org/10.1186/s12913-014-0563-8

Pryor, D.B. et al. 1985. Clinical data bases. Accomplishments and unrealized potential. *Medical care* 23(5), pp. 623–647. Available at: http://journals.lww.com/00005650-198505000-00020.

Public Health England 2017. *Chronic pain in adults 2017: Health Survey for England*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940858/Chronic_Pain_Report.pdf.

Public Health England. 2017. *Chapter 6: Social Determinants of Health*. Public Health England., pp. 60–79. Available at: https://www.gov.uk/government/publications/health-profile-for-england/chapter-6-social-determinants-of-health.

Public Health England. 2017. *Chronic pain in adults 2017: Health Survey for England*. London: Public Health England. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940858/Chronic_Pain_Report.pdf.

Public Health Scotland 2021. Data & intelligence from PHS. Available at: https://beta.isdscotland.org/ [Accessed: March 2021].

Public Health Scotland 2021. Prescriptions in the Community. Available at: https://www.opendata.nhs.scot/dataset/84393984-14e9-4b0d-a797-b288db64d088 [Accessed: March 2021].

Public Health Wales Observatory 2018. Health and its determinants in Wales. Available at: https://www2.nphs.wales.nhs.uk/PubHObservatoryProjDocs.nsf/61c1e930f9121fd080256f2a004937ed/99a9490d2e6d05268025820b005851de/$FILE/Health&determinantsinWales_Report_Eng.pdf [Accessed: 4 August 2021].

Public Health Wales Observatory 2020. Public Health Wales Observatory. Available at: http://www.publichealthwalesobservatory.wales.nhs.uk/measuring-inequalities-2016-files.

Puenpatom RA. Et al. 2012. Daily average consumption of 2 long-acting opioids: an interrupted time series analysis. Am Health Drug Benefits. 2012 Jan;5(1):52-60. PMID: 24991311; PMCID: PMC4046462.

Quality Watch et al. 2020. Poorest get worse quality of NHS care in England, new research finds. Available at: https://www.nuffieldtrust.org.uk/news-item/poorest-get-worse-quality-of-nhs-care-in-england-new-research-finds [Accessed: 13 March 2020].

Raffaeli, W. and Arnaudo, E. 2017. Pain as a disease: an overview. *Journal of pain research* 10, pp. 2003–2008. Available at: https://www.dovepress.com/pain-as-a-disease-an-overview-peer-reviewed-article-JPR.

Raftery, M.N. et al. 2011. Chronic pain in the Republic of Ireland--community prevalence, psychosocial profile and predictors of pain-related disability: results from the Prevalence, Impact

and Cost of Chronic Pain (PRIME) study, part 1. *Pain* 152(5), pp. 1096–1103. Available at: https://www.jpain.org/article/S1526-5900(11)00816-9/fulltext.

Raghavan, S. et al. 2011. New opioid side effects and implications for long-term therapy. *Trends in Anaesthesia and Critical Care* 1(1), pp. 18–21. doi: 10.1016/j.cacc.2010.06.003.

Rathbone, T. et al. 2020. Sex and gender considerations in low back pain clinical practice guidelines: a scoping review. *BMJ Open Sport & Exercise Medicine* 6(1), p. e000972. doi: 10.1136/bmjsem-2020-000972.

Reddy, K.S.K. et al. 2012. Human experimental pain models: A review of standardized methods in drug development. *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences* 17(6), pp. 587–595. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23626642&retmode=ref&cmd=prlinks.

Rennick, A. et al. 2016. Variability in opioid equivalence calculations. *Pain medicine (Malden, Mass.)* 17(5), pp. 892–898. Available at: https://academic.oup.com/painmedicine/article-lookup/doi/10.1111/pme.12920.

Rhudy, J.L. and Williams, A.E. 2005. Gender differences in pain: do emotions play a role? *Gender medicine* 2(4), pp. 208–226. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1550857905800518.

Rice, A.S.C. et al. 2016. Pain and the global burden of disease. *Pain* 157(4), pp. 791–796. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=26670465&retmode=ref&cmd=prlinks.

Richard, D.J.G.P. and Richard, P. 2012. The Economic Costs of Pain in the United States. *The Journal of Pain* 13(8), pp. 715–724. doi: 10.1016/j.jpain.2012.03.009.

Richards, G.C. et al. 2018. Effects of long-term opioid analgesics on cognitive performance and plasma cytokine concentrations in patients with chronic low back pain: a cross-sectional pilot study. *PAIN Reports* 3(4), pp. e669-7413.

Richards, G.C. et al. 2020a. Factors associated with the prescribing of high-dose opioids in primary care: a systematic review and meta-analysis. *BMC medicine* 18(1), p. 68. doi: 10.1186/s12916-020-01528-7.

Richards, G.C. et al. 2020b. Relation between opioid consumption and inclusion of opioids in 137 national essential medicines lists. *BMJ global health* 5(11). doi: 10.1136/bmjgh-2020-003563.

Riley, J.L. et al. 2001. Sex differences in negative emotional responses to chronic pain. *The Journal of Pain* 2(6), pp. 354–359. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1526590001862611.

Ringberg, U. et al. 2014. Examining the variation in GPs' referral practice: a cross-sectional study of GPs' reasons for referral. *The British journal of general practice : the journal of the Royal College of General Practitioners* 64(624), pp. e426-33. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24982495&retmode=ref&cmd=prlinks.

Rivat, C. and Ballantyne, J. 2016. The dark side of opioids in pain management: basic science explains clinical observation. *PAIN Reports* e570(1), pp. 1–9. doi: 10.1097/pr9<.0010000000000570.

Rocha, V. et al. 2017. Neighbourhood socioeconomic deprivation and health-related quality of life: A multilevel analysis. *PloS one* 12(12), pp. e0188736-16. Available at: https://dx.plos.org/10.1371/journal.pone.0188736.

Roberts, H. 2016. *Research Briefing: Misuse of prescription and over-the-counter medications*. Cardiff: National Assembly for Wales Research Service., p. 12. Available at: https://senedd.wales/media/irghgjnw/16-039-web-english.pdf.

Rodriguez, J. 2020. *Covid-19 and the Welsh economy: shutdown sectors and key workers*. Cardiff: Cardiff University. Available at: https://www.cardiff.ac.uk/__data/assets/pdf_file/0009/2409921/Covid_economy_report_1_Final_rep.pdf.

Rosner, B. et al. 2019. Opioid prescription patterns in Germany and the global opioid epidemic: Systematic review of available evidence. *PLOS ONE* 14(8), p. e0221153. Available at: https://doi.org/10.1371/journal.pone.0221153.

Routledge P. 2013. Personal Communication during Advisory Panel on Substance Misuse Evidence Gathering. Welsh Assembly Government.

Rovner, G.S. et al. 2017. Chronic pain and sex-differences; women accept and move, while men feel blue. *PLOS ONE* 12(4), p. e0175737. doi: 10.1371/journal.pone.0175737.

Royal Pharmaceutical Society of Great Britain. 2017. Medicines, Ethics, and Practice. Available at: http://books.google.co.uk/books?id=VhdtAAAAMAAJ&q=intitle:Medicines+Ethics+and+Practice&dq=intitle:Medicines+Ethics+and+Practice&hl=&cd=1&source=gbs_api.

Royal Pharmaceutical Society of Great Britain. 2021. *Medicines, Ethics, and Practice*. London: Pharmaceutical Press. Available at: https://www.rpharms.com/publications/the-mep.

Ruau, D. et al. 2012. Sex Differences in Reported Pain Across 11,000 Patients Captured in Electronic Medical Records. *The Journal of Pain* 13(3), pp. 228–234. Available at: http://dx.doi.org/10.1016/j.jpain.2011.11.002.

Ruscitto, A. et al. 2015. Changes in opioid and other analgesic use 1995–2010: Repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *European Journal of Pain* 19(1), pp. 59–66. doi: 10.1002/ejp.520.

Saariaho, T.H. et al. 2011. Early maladaptive schemas in Finnish adult chronic pain patients and a control sample. *Scandinavian journal of psychology* 52(2), pp. 146–153. Available at: http://doi.wiley.com/10.1111/j.1467-9450.2010.00849.x.

Sabatowski, R. et al. 2004. Pain Treatment: A Historical Overview. *Current Pharmaceutical Design* 10(7), pp. 701–716. doi: 10.2174/1381612043452974.

Sacks, D.W. et al. 2021. Can policy affect initiation of addictive substance use? Evidence from opioid prescribing. *Journal of health economics* 76, p. 102397. Available at: https://doi.org/10.1016/j.jhealeco.2020.102397.

Salas-Vega, S. et al. 2016. Big Data and Health Care: Challenges and Opportunities for Coordinated Policy Development in the EU. *Health Systems & Reform* 1(4), pp. 285–300. Available at: https://www.tandfonline.com/doi/full/10.1080/23288604.2015.1091538.

Salas, J. et al. 2017. New-onset depression following stable, slow, and rapid rate of prescription opioid dose escalation. *Pain* 158(2), pp. 306–312. doi: 10.1097/j.pain<.0010000000000763.

Salas, J. et al. 2020. The association of opioid use duration and new depression episode among patients with and without insomnia. *Journal of opioid management* 16(5), pp. 317–328. doi: 10.5055/jom.2020.0587.

SAS Institute Inc 2021. SAS 9.4 Ink. Available at: https://www.sas.com/en_gb/home.html?gclid=Cj0KCQjwssyJBhDXARIsAK98ITTEFxlhVtulGrJOHlxbouBdIYi556GES_Id8FfmuAKSj7c7sLkKPN4aAkMKEALw_wcB [Accessed: 2 June 2021].

Schatman, M.E. and Shapiro, H. 2019. Damaging State Legislation Regarding Opioids: The Need to Scrutinize Sources of Inaccurate Information Provided to Lawmakers. *Journal of pain research* 12, pp. 3049–3053. Available at: https://www.dovepress.com/damaging-state-legislation-regarding-opioids-the-need-to-scrutinize-so-peer-reviewed-article-JPR.

Schatman, M.E. et al. 2016. The MEDD myth: the impact of pseudoscience on pain research and prescribing-guideline development. *Journal of pain research* Volume 9, pp. 153–4. Available at: https://www.dovepress.com/the-medd-myth-the-impact-of-pseudoscience-on-pain-research-and-prescri-peer-reviewed-article-JPR.

Scherrer, J.F. et al. 2016. Increased Risk of Depression Recurrence After Initiation of Prescription Opioids in Noncancer Pain Patients. *The Journal of Pain* 17(4), pp. 473–482. Available at: https://www.sciencedirect.com/science/article/pii/S1526590015010007.

Scherrer, J.F. et al. 2016. Prescription Opioid Duration, Dose, and Increased Risk of Depression in 3 Large Patient Populations. *The Annals of Family Medicine* 14(1), pp. 54–62. doi: 10.1370/afm.1885.

Schieber, L.Z. et al. 2020. Variation in Adult Outpatient Opioid Prescription Dispensing by Age and Sex — United States, 2008–2018. *MMWR. Morbidity and Mortality Weekly Report* 69(11), pp. 298–302. doi: 10.15585/mmwr.mm6911a5.

Schifanella, R. et al. 2020. Spatial heterogeneity and socioeconomic determinants of opioid prescribing in England between 2015 and 2018. *BMC Medicine* 18(1), pp. 127–13. Available at: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01575-0.

Schofferman, J. 2006. Restoration of Function: The Missing Link in Pain Medicine? *Pain medicine (Malden, Mass.)* 7, pp. S159–S165. Available at: https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1526-4637.2006.00131.x.

Schofield, P. 2012. Pain in Older Adults: Epidemiology, Impact and Barriers to Management. *Reviews in Pain* 1(1), pp. 12–14.

Schofield, P. 2017. Pain management in older adults. *Medicine* 45(1), pp. 41–45. Available at: http://dx.doi.org/10.1016/j.mpmed.2016.10.005.

Schofield, P. and Abdulla, A. 2018. Pain assessment in the older population: what the literature says. *Age and ageing* 47(3), pp. 324–327. Available at: https://academic.oup.com/ageing/article/47/3/324/4951960.

Scholz, J. et al. 2019. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain* 160(1), pp. 53–59. Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.7.aspx.

Schug, S.A. et al. 2016. Acute pain management: scientific evidence, fourth edition, 2015. *The Medical Journal of Australia* 204(8), pp. 315–317. doi: 10.5694/mja16.00133.

Schug, S.A. et al. 2019. The IASP classification of chronic pain for ICD-11. *PAIN* 160(1), pp. 45–52. doi: 10.1097/j.pain<.0010000000001413.

Scioli-Salter, E.R. et al. 2015. The shared neuroanatomy and neurobiology of comorbid chronic pain and PTSD: therapeutic implications. *The Clinical journal of pain* 31(4), pp. 363–374. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=24806468&retmode=ref&cmd=prlinks.

Scott-Thomas, S. 2020. *Personal Communication.* Discussion about national and local guideline implementation.

Scottish Affairs Select Committee 2019. *Problem drug use in Scotland*. UK Parliament. Available at: https://publications.parliament.uk/pa/cm201919/cmselect/cmscotaf/44/4405.htm#_idTextAnchor006.

Scottish Government 2021. Policy - Social care. Available at: https://www.gov.scot/policies/social-care/health-and-social-care-integration/ [Accessed: 3 August 2021].

Scottish Intercollegiate Guideline Network SIGN 2019. Management of Chronic Pain. Available at: https://www.sign.ac.uk/media/1108/sign136_2019.pdf [Accessed: 15 September 2020].

Secure Anonymised Information Linkage (SAIL) Databank. 2021. The SAIL databank. Available at: https://saildatabank.com/. [Accessed: 24 August 2021].

Secure Anonymised Information Linkage Databank 2021. The SAIL databank. Available at: https://saildatabank.com/ [Accessed: 16 June 2021].

Sellick, J. 2018. How can we build a rural health and care workforce. Available at: https://www.rsnonline.org.uk/how-can-we-build-a-rural-health-and-care-workforce.

Seyfried, O. and Hester, J. 2012. Opioids and endocrine dysfunction. *British Journal of Pain* 6(1), pp. 17–24. doi: 10.1177/2049463712438299.

Shafrin, J. 2008. Welfarists vs. Extra-welfarists. Available at: https://www.healthcare-economist.com/2008/02/13/welfarists-vs-extra-welfarists/ [Accessed: 29 January 2021].

Shah, A. et al. 2017. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR. Morbidity and Mortality Weekly Report* 66(10), pp. 265–269. doi: 10.15585/mmwr.mm6610a1.

Shaheen, P.E. et al. 2009. Opioid Equianalgesic Tables: Are They All Equally Dangerous? *Journal of Pain and Symptom Management* 38(3), pp. 409–417. doi: 10.1016/j.jpainsymman.2009.06.004.

Shared Services Partnership, NHS Wales 2021. General Practice Prescribing Data Extract. Available at: https://nwssp.nhs.wales/ourservices/primary-care-services/general-information/data-and-publications/general-practice-prescribing-data-extract/ [Accessed: August 2021].

Shared Services Partnership, NHS Wales. CASPA data. Available at: https://nwssp.nhs.wales/ourservices/primary-care-services/our-latest-news/caspa-data-december-2020/ [Accessed: August 2021].

Sharma, S. et al. 2019. Health system strengthening is needed to respond to the burden of pain in low- and middle-income countries and to support healthy ageing. *Journal of global health* 9(2), p. 020317. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=33274068&retmode=ref&cmd=prlinks.

Shaw, K. and Fudin, J. 2013. Evaluation and comparison of online equianalgesic opioid dose conversion calculators. *paindr.com* , pp. 61–66.

Sicular, S. 2013. Gartner's Big Data Definition Consists of Three Parts, Not to Be Confused with Three "V"s. Available at: https://www.forbes.com/sites/gartnergroup/2013/03/27/gartners-big-data-definition-consists-of-three-parts-not-to-be-confused-with-three-vs/ [Accessed: January 2021].

Silversides, A. 2011. Use of strong opioids in Canada rose sharply between 2005 and 2010. *British Medical Journal* 343(aug25 2), p. d5441. doi: 10.1136/bmj.d5441.

Singer, J.A. et al. 2019. Today's nonmedical opioid users are not yesterday's patients; implications of data indicating stable rates of nonmedical use and pain reliever use disorder. *Journal of pain research* 12, pp. 617–620. Available at: https://www.dovepress.com/todays-nonmedical-opioid-users-are-not-yesterdays-patients-implication-peer-reviewed-article-JPR.

Smith, B.H. and Torrance, N. 2012. Epidemiology of Neuropathic Pain and Its Impact on Quality of Life. *Current pain and headache reports* 16(3), pp. 191–198. Available at: http://link.springer.com/10.1007/s11916-012-0256-0.

Smith, B.H. et al. 2019. The IASP classification of chronic pain for ICD-11: applicability in primary care. *PAIN* 160(1), pp. 1–5. doi: 10.1097/j.pain<.0010000000001360. Available at: https://journals.lww.com/pain/Fulltext/2019/01000/The_IASP_classification_of_chronic_pain_for.11.aspx.

Smith, B.H. et al. 2021. Drugs for chronic pain - we still need them. Available at: https://bjgplife.com/2021/02/02/drugs-for-chronic-pain-we-still-need-them/.

Smith, E. et al. 2014. The global burden of other musculoskeletal disorders: estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases* 73(8), pp. 1462–1469. Available at: http://ard.bmj.com/cgi/doi/10.1136/annrheumdis-2013-204680.

Smith, J. 2005. The Shipman Inquiry. Available at: https://webarchive.nationalarchives.gov.uk/ukgwa/20090808155005/http://www.the-shipman-inquiry.org.uk/home.asp. [Accessed: 24 January 2018].

Smith, S.R. et al. 2017. Cost-Effectiveness of Tramadol and Oxycodone in the Treatment of Knee Osteoarthritis. *Arthritis Care & Research* 69(2), pp. 234–242. doi: 10.1002/acr.22916.

Solà, I. et al. 2019. Quality of life and well-being from the perspective of patients on opioid agonist maintenance treatment: study protocol for a systematic review of qualitative research and a scoping review of measures. *Systematic Reviews* 8(1), pp. 1–7. doi: 10.1186/s13643-019-1237-8.

Sorge, R.E. and Strath, L.J. 2018. Sex differences in pain responses. *Current Opinion in Physiology* 6, pp. 75–81. Available at: https://linkinghub.elsevier.com/retrieve/pii/S2468867318300786.

Spooner,.L. et al. 2016. "High-Dose Opioid Prescribing and Opioid- Related Hospitalization: A Population-Based Study," pp. 1–12. doi:https://doi.org/10.1371/journal.pone.0170834. Accessed at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0167479.
Sproule, B. 2015. Prescription monitoring programs in Canada: best practice and program review. Available at: http://nperesource.casn.ca/wp-content/uploads/2017/01/CCSA-Prescription-Monitoring-Programs-in-Canada-Report-2015-en.pdf.

Stannard, C. 2018a. Where now for opioids in chronic pain? *Drug and therapeutics bulletin* 56(10), pp. 118–122. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30254063&retmode=ref&cmd=prlinks.

Stannard, C.F. 2018b. Pain and pain prescribing: what is in a number? *British journal of anaesthesia* 120(6), pp. 1147–1149. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0007091218301806.

Stanos,S. 2016. Rethinking chronic pain in a primary care setting, Postgraduate Medicine, 128:5, 502-515, doi: 10.1080/00325481.2016.1188319

StatsWales 2010. *Welsh Index of Multiple Deprivation - LSOA maps 2011*. Available at: https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation/Archive/LSOA-Maps [Accessed: July 26, 2019].

StatsWales 2010. Welsh Index of Multiple Deprivation 2011 by rank and local super output area. Available at: https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation/Archive/WIMD-2011/wimd2011 [Accessed: 12 May 2021].

StatsWales 2019. Population estimates by local authority and year. Available at: https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/Local-Authority/populationestimates-by-localauthority-year.

StatsWales 2019. WIMD 2019. Available at: https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation/WIMD-maps-2019. [Accessed: 24 July 2021].

StatsWales 2020. Ethnicity by area and ethnic group. Available at: https://statswales.gov.wales/Catalogue/Equality-and-Diversity/Ethnicity/ethnicity-by-area-ethnicgroup [Accessed: November 2020].

StatsWales 2020. General health and illness by year. Available at: https://statswales.gov.wales/catalogue/National-Survey-for-Wales/Population-Health/Adult-general-health-and-illness/genhealthillness-by-year [Accessed: December 2020].

Steel, N. et al. 2018. Changes in health in the countries of the UK and 150 English Local Authority areas 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* 392(10158), pp. 1647–1661. doi: 10.1016/s0140-6736(18)32207-4.

Stewart, G. and Basler, M.H. 2013. Wanted: national monitoring system for long term opioids. *British Medical Journal* 347(f5586), p. 22.

Stilwell, P. and Harman, K. 2019. An enactive approach to pain: beyond the biopsychosocial model. *Phenomenology and the Cognitive Sciences* 18(4), pp. 1–29. doi: 10.1007/s11097-019-09624-7.

Stoicea, N. et al. 2019. Current perspectives on the opioid crisis in the US healthcare system. *Medicine* 98(20), pp. e15425-8. Available at: http://journals.lww.com/00005792-201905170-00010.

Stubbs, B. et al. 2014a. Pain and the Risk for Falls in Community-Dwelling Older Adults: Systematic Review and Meta-Analysis. *Archives of Physical Medicine and Rehabilitation* 95(1), pp. 175-187.e9. doi: 10.1016/j.apmr.2013.08.241.

Stubbs, B. et al. 2014b. Pain is associated with recurrent falls in community-dwelling older adults: evidence from a systematic review and meta-analysis. *Pain Medicine* 15(7), pp. 1115–1128. doi: 10.1111/pme.12462.

Sullivan, M.D. and Ballantyne, J.C. 2016. Must we reduce pain intensity to treat chronic pain? *PAIN* 157(1), pp. 65–69. doi: 10.1097/j.pain<.0010000000000336.

Sullivan, M.D. et al. 2008. Trends in use of opioids for non-cancer pain conditions 2000–2005 in Commercial and Medicaid insurance plans: The TROUP study. *Pain* 138(2), pp. 440–449. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006396-200808310-00022.

Sullivan, M.J.L. et al. 2000. Gender differences in pain and pain behavior: The role of catastrophizing. *Cognitive Therapy and Research* 24(1), pp. 121–134. Available at: http://en.wikipedia.org/wiki/Anxiety.

Sutherland, K. and Coyle, N. 2009. *Quality in Healthcare in England, Wales, Scotland and Northern Ireland: an intra-UK chartbook*. London: The Health Foundation. Available at: www.health.org.uk.

Svendsen, K. et al. 2011. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. *Palliative medicine* 25(7), pp. 725–732. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21378066&retmode=ref&cmd=prlinks.

Takura, T. et al. 2015. The societal burden of chronic pain in Japan: an internet survey. *Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association* 20(4), pp. 750–760. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25963609&retmode=ref&cmd=prlinks.

Takura, T. et al. 2021. Cost-Effectiveness Analysis of the Treatment Strategies with or without Opioid Medications in Surgery-Eligible Patients with Osteoarthritis in Japan. *PharmacoEconomics - Open* , pp. 1–13. doi: 10.1007/s41669-021-00292-5.

Tan, E.C. et al. 2015. Analgesic Use and Daytime Sleepiness in Residents with and Without Dementia in Residential Aged Care Facilities. *Drugs & Aging* 32(12), pp. 1045–1053. Available at: https://doi.org/10.1007/s40266-015-0325-2.

Taylor, M. and Filby, A. 2014. What is sensitivity analysis? Available at: https://www.whatisseries.co.uk/what-is-sensitivity-analysis/.

Taylor, S. et al. 2019. *Dependence and withdrawal associated with some prescribed medicines: an evidence review.* London: Public Health England. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940255/PHE_PMR_report_Dec2020.pdf.

Techtarget 2021. SQL definition. Available at: http://searchsqlserver.techtarget.com/definition/SQL [Accessed: 11 July 2017].

Terplan, M. 2017. Women and the opioid crisis: historical context and public health solutions. *Fertility and sterility* 108(2), pp. 195–199. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0015028217304314.

Thakral, M. et al. 2018. Comparing Pain and Depressive Symptoms of Chronic Opioid Therapy Patients Receiving Dose Reduction and Risk Mitigation Initiatives with Usual Care. *The Journal of Pain* 19(1), pp. 111–120. doi: 10.1016/j.jpain.2017.09.006.

The Joseph Rowntree Foundation Analysis Unit 2017. UK Poverty 2017: A comprehensive analysis of poverty trends and figures. York: Joseph Rowntree Foundation, p. 113. Available at: https://www.jrf.org.uk/report/uk-poverty-2017.

The What is …? series. 2014. Available at: www.whatisseries.co.uk. [Accessed: September 2020]

Thielke, S.M. et al. 2017. A Prospective Study of Predictors of Long-term Opioid Use Among Patients with Chronic Noncancer Pain. *The Clinical journal of pain* 33(3), p. 198. Available at: http://journals.lww.com/clinicalpain/Fulltext/2017/03000/A_Prospective_Study_of_Predictors_of_Long_term.2.aspx.

Thiru, K. et al. 2003. Systematic review of scope and quality of electronic patient record data in primary care. *British Medical Journal* 326(7398), p. 1070. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=12750210&retmode=ref&cmd=prlinks.

Todd, A. et al. 2018. The Pain Divide: a cross-sectional analysis of chronic pain prevalence, pain intensity and opioid utilisation in England. *BMJ open* 8(7), p. e023391. doi: 10.1136/bmjopen-2018-023391.

Torrance, N. et al. 2014. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: Does the choice between the EQ-5D and SF-6D matter? *Pain* 155(10), pp. 1996–2004. Available at: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006396-201410000-00016.

Torrance, N. et al. 2018. Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study. *British journal of anaesthesia* 120(6), pp. 1345–1355. Available at: https://linkinghub.elsevier.com/retrieve/pii/S000709121830134X.

Torrance, N. et al. 2020. Trends in gabapentinoid prescribing, co-prescribing of opioids and benzodiazepines, and associated deaths in Scotland. *British journal of anaesthesia* 125(2), pp. 159–167. doi: 10.1016/j.bja.2020.05.017.

Tracey, I. 2016. Finding the Hurt in Pain. *Cerebrum* (cer-15-16), pp. 1–12. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5501013/.

Tracey, I. and Mantyh, P.W. 2007. The cerebral signature for pain perception and its modulation. *Neuron* 55(3), pp. 377–391. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17678852&retmode=ref&cmd=prlinks.

Trawalter, S. et al. 2012. Racial bias in perceptions of others' pain. *PloS one* 7(11), p. e48546. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0048546.

Treede, R.-D. et al. 2015. A classification of chronic pain for ICD-11. *Pain* 156(6), pp. 1003–1007. doi: 10.1097/j.pain<.0010000000000160.

Treede, R.-D. et al. 2019. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* 160(1), pp. 19–27. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=30586067&retmode=ref&cmd=prlinks.

Trescot, A.M. *et al.* 2008. Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain physician*, 11(2 Suppl), pp. S181-200. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18443639&retmode=ref&cmd=prlinks.

Tsang, A. et al. 2008. Common Chronic Pain Conditions in Developed and Developing Countries: Gender and Age Differences and Comorbidity with Depression-Anxiety Disorders. *Journal of Pain* 9(10), pp. 883–891. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1526590008005750.

Turk, D.C. et al. 2016. Assessment of Psychosocial and Functional Impact of Chronic Pain. *The Journal of Pain* 17(9 Suppl), pp. T21-49. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27586830&retmode=ref&cmd=prlinks.

Turner, D. et al. 2019. Harm Reduction Database Wales: Drug related mortality Annual Report 2018-19. Cardiff, Wales: Public Health Wales. Available at: https://phw.nhs.wales/news/drug-deaths-at-their-highest-ever-levels-in-wales/harm-reduction-database-wales-drug-related-mortality-annual-report-2018-19/.

Turunen, E. and Hiilamo, H. 2014. Health effects of indebtedness: a systematic review. *BMC Public Health* 14(1), pp. 1323–8. Available at: http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-14-489.

Tzartzas, K. et al. 2019. General practitioners referring patients to specialists in tertiary healthcare: a qualitative study., pp. 1–9. doi: 10.1186/s12875-019-1053-1.

van den Beuken-van Everdingen, M.H.J. et al. 2013. Prolonged QT interval by methadone: Relevance for daily practice? A prospective study in patients with cancer and noncancer pain. *Journal of Opioid Management* 9(4). doi: https://doi.org/10.5055/jom.2013.0167.

Velayudhan, A. et al. 2014. Opioid-induced hyperalgesia. *Continuing Education in Anaesthesia, Critical Care and Pain* 14(3), pp. 125–129. Available at: https://www.scopus.com/inward/record.uri?partnerID=HzOxMe3b&scp=84900564622&origin=inward.

Verhamme, K.M.C. and Bohnen, A.M. 2019. Comment Are we facing an opioid crisis in Europe? *The Lancet Public Health* 4 KW-(10), pp. e483–e484.

Vincent, K. and Tracey, I. 2008. Hormones and their Interaction with the Pain Experience. *Reviews in pain* 2(2), pp. 20–24. Available at: http://journals.sagepub.com/doi/10.1177/204946370800200206.

Vokinger, K.N. 2018. Opioid Crisis in the US - Lessons from Western Europe. *The Journal of law, medicine & ethics : a journal of the American Society of Law, Medicine & Ethics* 46(1), pp. 189–190. doi: 10.1177/1073110518766033.

Vos, T. et al. 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* 390(10100), pp. 1211–1259. Available at: http://www.thelancet.com/article/S0140673617321542/fulltext.

Vos, T. et al. 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990 - 2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 396(10258), pp. 1204–1222. Available at: http://dx.doi.org/10.1016/S0140-6736(20)30925-9.

Wagemaakers, F.N. et al. 2017. Opioid analgesic use in Australia and The Netherlands: a cross-country comparison. *International Journal of Clinical Pharmacy* 39(4), pp. 874–880. Available at: http://link.springer.com/10.1007/s11096-017-0492-9.

Walley, T. and Roberts, D. 2000. Average daily quantities: a tool for measuring prescribing volume in England. *Pharmacoepidemiology and Drug Safety* 9(1), pp. 55–8. Available at: https://onlinelibrary.wiley.com/doi/pdf/10.1002/%28SICI%291099-1557%28200001/02%299%3A1%3C55%3A%3AAID-PDS467%3E3.0.CO%3B2-H.

Walsh, E. and National Welsh Informatics Service (NWIS) - Information Services, 2019. Treatment Data - Substance Misuse in Wales 2018-19. Available at: https://gov.wales/sites/default/files/publications/2019-10/treatment-data-substance-misuse-in-wales-2018-19.pdf.

Wang, W. and Krishnan, E. 2014. Big Data and Clinicians: A Review on the State of the Science. *JMIR medical informatics* 2(1), pp. e1-11. Available at: http://www.medinform.jmir.org/2014/1/e1/.

Warraich, H.J. 2021. Why men and women feel pain differently. *The Washington Post* 15 May. Available at: https://www.washingtonpost.com/health/women-and-pain/2021/05/14/98cb4116-9d55-11eb-9d05-ae06f4529ece_story.html.

Warth, J. et al. 2019. Over-indebtedness and its association with pain and pain medication use. *Preventive Medicine Reports* 16, p. 100987. Available at: https://www.sciencedirect.com/science/article/pii/S2211335519301585.

Weesie, Y.M. et al. 2020. Use of Opioids Increases with Age in Older Adults: An Observational Study (2005–2017)., pp. 1–8. doi: 10.3389/fphar.2020.00648/full.

Weisberg, D. and Stannard, C. 2013. Lost in translation? Learning from the opioid epidemic in the USA. *Anaesthesia* 68(12), pp. 1215–1219. doi: 10.1111/anae.12503.

Welsh Analytical Prescribing Support Unit (2013) *NHS Wales Primary Care Prescribing Analysis: Tramadol*. Cardiff: All Wales Therapeutics and Toxicology Centre. Available at: https://awmsg.nhs.wales/files/prescribing-analysis/primary-care-prescribing-analysis-tramadol-pdf/.

Welsh Assembly Government 2008. *Designed for People with Chronic Conditions*. Cardiff: Welsh Assembly Government. Available at: http://www.wales.nhs.uk/documents/chronicpaine.pdf.

Welsh Government 2011. Welsh Index of Multiple deprivation 2011., pp. 1–15. Available at: https://gov.wales/welsh-index-multiple-deprivation-full-index-update-ranks-2011.

Welsh Government 2016. Key Industries. Available at: https://tradeandinvest.wales/key-industries [Accessed: 5 November 2020].

Welsh Government 2019. Welsh Index of Multiple Deprivation 2019. Available at: https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation/WIMD-2019 .

Welsh Government 2019a. *A Healthier Wales*. Welsh Government. Available at: https://gov.wales/sites/default/files/publications/2019-10/a-healthier-wales-action-plan.pdf [Accessed 19 March 2021]

Welsh Government 2019b. *Living with Persistent Pain in Wales*. Welsh Government. Available at: https://gov.wales/sites/default/files/publications/2019-05/living-with-persistent-pain-in-wales.pdf [Accessed: 24 February 2021].

Welsh Government 2021. National Institute for Health and Care Excellence (NICE) guidelines. Available at: https://gov.wales/national-institute-health-and-care-excellence-nice-guidelines [Accessed: 10 August 2021].

Welsh Government and NHS Wales 2016. Prudent Healthcare. Available at: https://gov.wales/sites/default/files/publications/2019-04/securing-health-and-well-being-for-future-generations.pdf.

Welsh Government and Statistics for Wales 2020. *Prescriptions in Wales, 2019-20*. Available at: https://gov.wales/sites/default/files/statistics-and-research/2020-09/prescriptions-wales-april-2019-march-2020-610.pdf.

Welsh Government and Statistics for Wales 2021. Prescriptions in Wales: interactive dashboard. Available at: https://gov.wales/prescriptions-wales-interactive-dashboard.

Welzel, F.D. et al. 2017. Frequent attenders in late life in primary care: a systematic review of European studies., pp. 1–14. doi: 10.1186/s12875-017-0700-7.

Wen, L.S. and Sadeghi, N.B. 2020. The opioid crisis and the 2020 US election: crossroads for a national epidemic. *Lancet* 396(10259), pp. 1316–1318. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0140673620321139.

Wenig, C.M. et al. 2009. Costs of back pain in Germany. *European Journal of Pain* 13(3), pp. 280–286. Available at:

http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=18524652&retmode=ref&cmd=prlinks.

Whitehead, M. et al. 2021. Poverty, health, and covid-19. *British Medical Journal* 372(n376), pp. n376-2. Available at: https://www.bmj.com/content/372/bmj.n376.abstract.

WHO Collaborating Centre for Drug Statistics Methodology 2021. International language for drug utilization research. Available at: https://www.whocc.no [Accessed: 2 September 2021].

Whynes, D.K. 2008. Deprivation and self-reported health: are there "Scottish effects" in England and Wales? *Journal of Public Health* 31(1), pp. 147–153. doi: 10.1093/pubmed/fdn089.

Wiffen, P.J. et al. 2017. Opioids for cancer pain - an overview of Cochrane reviews. Pain, C. et al. eds. *Cochrane Database of Systematic Reviews* 168(10), pp. 1102–23. doi: 10.1002/14651858.cd012592.pub2.

Wilkerson, R.G. et al. 2016. The Opioid Epidemic in the United States. *Emergency medicine clinics of North America* 34(2), pp. e1–e23. Available at: http://linkinghub.elsevier.com/retrieve/pii/S073386271500108X.

Williams, A.C. de C. 2021. Women's pain is routinely underestimated, and gender stereotypes are to blame - new research. Available at: https://theconversation.com/womens-pain-is-routinely-underestimated-and-gender-stereotypes-are-to-blame-new-research-158599 [Accessed: 7 July 2021].

Wilsey, B. and Prasad, H. 2012. Real-time access to prescription drug monitoring databases. *Canadian Medical Association Journal* 184(16), pp. 1767–1768. Available at: http://www.cmaj.ca/cgi/doi/10.1503/cmaj.121495.

Wilson, M.N. et al. 2019. Effectiveness of Prescription Monitoring Programs in Reducing Opioid Prescribing, Dispensing, and Use Outcomes: A Systematic Review. *The Journal of Pain* 20(12), pp. 1383–1393. Available at: https://doi.org/10.1016/j.jpain.2019.04.007.

Wolf, A. et al. 2019. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *International journal of epidemiology* 48(6), pp. 1740–1740g. Available at: https://academic.oup.com/ije/article/48/6/1740/5374844.

World Health Organisation 2019. WHO Model Lists of Essentials Medicines. Available at: https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists [Accessed: 2 April 2021].

World Health Organization WHO 2021. WHO's cancer pain ladder for adults. *WHO*. Available at: http://www.who.int/cancer/palliative/painladder/en/.

Wu, A. et al. 2020. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. *Annals of translational medicine* 8(6), pp. 299–299. Available at: https://atm.amegroups.com/article/view/38037/html.

Yarborough, B.J.H. et al. 2016. Understanding opioid overdose characteristics involving prescription and illicit opioids: A mixed methods analysis. *Drug and alcohol dependence* 167, pp. 49–56. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0376871616302216.

Zhang, L. et al. 2021. Gender biases in estimation of others' pain. *The Journal of Pain* . doi: 10.1016/j.jpain.2021.03.001.

Zin, C.S. et al. 2014. Changes in trends and pattern of strong opioid prescribing in primary care. *European Journal of Pain* 18(9), pp. 1343–1351. Available at: https://nottingham-repository.worktribe.com/output/1100471.

Zingmond, D.S. et al. 2004. Linking hospital discharge and death records—accuracy and sources of bias. *Journal of Clinical Epidemiology* 57(1), pp. 21–29. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0895435603002506.

Zis, P. et al. 2017. Depression and chronic pain in the elderly: links and management challenges. *Clinical Interventions in Aging* Volume 12, pp. 709–720. Available at: https://www.dovepress.com/depression-and-chronic-pain-in-the-elderly-links-and-management-challe-peer-reviewed-article-CIA

Appendices

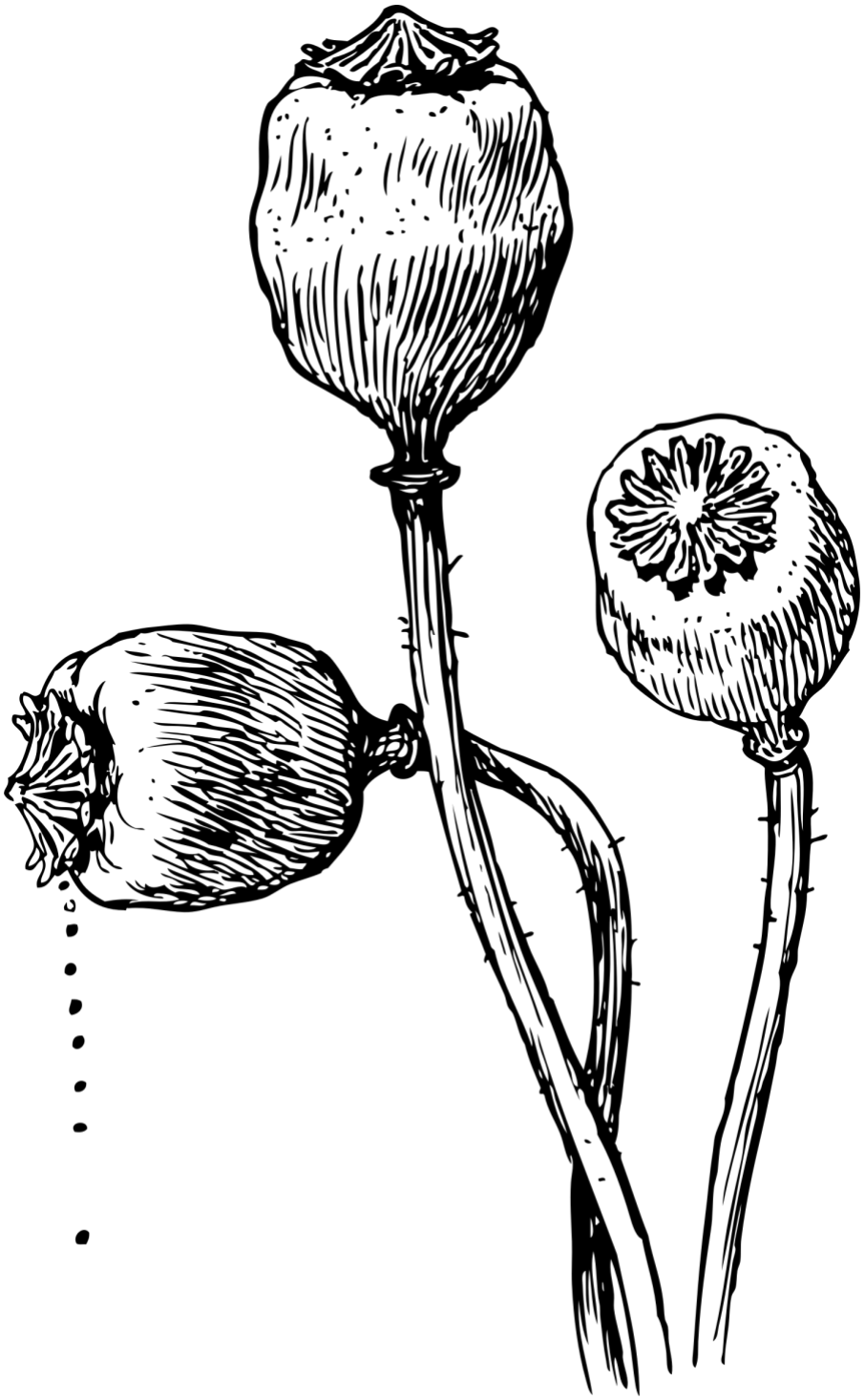


Table of Contents

List of Appendix tables

List of Appendix figures

Appendix A Methods

A.1 SAIL Application form

Secure Anonymised Information Linkage (SAIL) Information Governance Review Panel (IGRP) Application Form

SAIL IGRP Application Form

The following form has been designed to collect the information needed for the information governance approval process for work involving the SAIL databank. The information you provide will facilitate consideration of your enquiry. Guidance notes on completing this form can be found at:
http://www.saildatabank.com/media/25300/Guidance_Notes_for_SAIL_IGRP_Application.docx

SAIL Feasibility Agreement

All projects require a SAIL Feasibility Agreement to be completed and signed before proceeding to IGRP. This agreement will have been developed as part of the initial project scoping process with a senior SAIL analyst. Do not continue with this form until you have had your project scoping discussion.

Please provide the agreement number: **0507**

1a. Provide contact details of project lead:

Name: Emma Davies
Job title: Advanced Pharmacy Practitioner in Pain Management / PhD student
Organisation: Abertawe Bro Morgannwg University Health Board / Swansea University
Address: [redacted], College of Human and Health Sciences, Swansea University, Singleton Campus
Tel: [redacted]
Fax:
Email: [redacted]

1b. Provide contact details of the lead contact from any other organisation who will be accessing the data:

	Name	Job title	Organisation
1			
2			
3			
4			

2. Provide full title of the project: Trends in Opioid Prescribing and Associated Resource Utilisation in Wales (TOPAS)

3. Provide details on who is commissioning the project:

PhD project – Swansea University, SCHE – PhD fellowship is funded by Swansea University and RCBC

Research monies funded by a personal research grant from Pharmacy Research UK

4. Provide the aim of the project, including anticipated outcomes:

Please include a copy of the protocol/plan for the proposed work with SAIL, including the contact details of any co-applicants when you return your completed form.

This study aims to:

- Describe the trends of opioid prescribing in the Welsh Primary Care Population, over a 10-year period (2005 – 2015)
- Determine any causal or potential association between opioid use, non-pain morbidities and the utilisation of other health care services, in primary, community or acute care settings
- Develop an economic evaluation that enables the full costs of opioid use in chronic, non-cancer pain to be more accurately determined.

5. Provide a lay summary of the project:

Opioids are drugs, derived directly from or related to the naturally occurring alkaloids found in the opium poppy (*papaver somniferum*). Traditionally, opioids have been used to treat pain following trauma and surgery and also in the management of pain due to cancer and at the end of life.

In the last twenty to thirty years, there has been increasing use of opioids for the long-term treatment of chronic, non-cancer pain (CNCP), arising from conditions such as osteoarthritis, low back pain and fibromyalgia. This is despite the medical evidence being limited to short-term benefits and side effects of these drugs. Much less is known about the effectiveness and safety of opioids when given over longer treatment periods and in high doses for non-cancer pain.

Scientific literature and national media in the United Kingdom have expressed concern about whether the known increase in opioid prescribing will lead to increased incidence of dependence and misuse. Studies from North America suggest that patients taking opioids use more healthcare resources than other patients(Kern et al. 2015; Wilkerson et al. 2016) and may have a higher death rate than non-users (Yarborough et al. 2016).

In Wales, there are similar concerns following several years of increasing numbers of deaths involving opioid medications and a general upwards trend in opioid prescribing. Insight into the consequences of chronic non-cancer pain, particularly focussed on the use of opioids, has been little studied in the general public or 'patients'. Numerous studies have enquired into clinician's perceptions of chronic pain, how it is best managed and the prescribing and safety of opioid medication within that context. However, to date, there has not been a large-scale, observational study assessing the actual patterns of opioid use in clinical practice over extended periods of time nor if any link exists between the use of these drugs and other health care utilisation.

This study, therefore, aims to describe the use of opioids in all Welsh patients prescribed them and whose data is available via a national repository. The prescribing patterns and clinical outcomes, including all interactions with health care services across sectors will be evaluated in order to determine if there is an association between opioid use and health care utilisation.

From this, the intention is to establish an economic estimation that of the real costs of opioid use in chronic, non-cancer pain.

6. Provide an outline of the public engagement strategy for the study, or a brief explanation why there is not public engagement:
This study evaluates established medical interventions requiring no patient user group involvement in this instance. It is envisaged that further work will be developed from this project, and which would require patient and public involvement.

7. Provide information on the relevant permissions you have obtained or that are being sought:

	Obtained	*Being sought*
Not required		
Research ethics [☒]	[☐]	[☐]

Please state the name of the committee that is being applied to/ has given approval, as applicable:
Research ethics committee:

If you have ticked 'not required' please specify the reasons:
☒ The project will use only anonymised data, and therefore research ethics review is not required.
☐ Other:

	Obtained	*Being sought*	*Not required*
Independent peer review	[☒]	[☐]	[☐]

Please state the name of the peer reviewer that is being applied to/ has given approval, as applicable:
Peer reviewer: **The research protocol underwent peer review by Pharmacy Research UK as part of the grant application process**

If you have ticked 'not required' please specify the reasons:
☒ The project will use only anonymised data, and therefore independent review is not required.
☐ Other:

	Obtained	*Being sought*	*Not required*
Permission from data-holding Organisation to use their datasets	[☐]	[☐]	[☒]

Please state the name of the data provider that is being applied to/ has given approval, as applicable:
Data organisation:

If you have ticked 'not required' please specify the reasons.
☒ The project uses only SAIL unrestricted core datasets and/or data held by the project.
☐ Other:

Please note that it is the responsibility of the project lead to ensure that the relevant permissions are obtained.

8a. Provide a prospective start date for the work involving SAIL: 01/11/2016

8b. Provide anticipated end date of the project: (End date OR time duration after approval)
01/10/2020 (proposed date for thesis submission)

9a. Provide details of data you require access to for the proposed work with SAIL?
Please list:
The SAIL datasets you require information from
Welsh Demographic Service
GP Event data
Patient Episode Database Wales
Accident and Emergency room data
Outpatient data
ONS Mortality data

The information needed from each dataset

<u>Welsh Demographic Service</u>
Patient week of birth, gender code, date of death, address and registration history for all Wales population from 2005 to 2015, (to establish event recording completeness for a case cohort and matched controls). To Include LSOA derived Welsh Index of Multiple Deprivation scores and Health Board of residence for each residency period.

GP Event data
Event code, event date, event value

Patient Episode Database Wales
All in patient and day-case hospital activity for the opiate cohort and suitably defined control group including admission dates, discharge dates, lengths of stay, diagnoses, operative procedures, method of admission, elective or non-elective flag, outcomes in terms of discharge destination. Including all fields required to establish linkage between the spell, diagnosis and episode tables, and to establish episode and diagnostic sequencing. Also, to include FRG based costing information for each item of activity (This could be provided after the establishment of suitable cases and matched control cohorts rather than providing the whole of Wales dataset).

Accident and Emergency room data
Date of attendance, date of incidence, method of arrival, injury and accident detail, discharged to home or admitted to hospital flag (to be used for costing purposes).

Outpatients data
Dates of attendance, first or repeat attendance flag, specialty of attendance, non-attendance

ONS Mortality data
Date of death, primary cause of death, secondary cause of death.

Please indicate the time period for which data is requested
We will be analysing a cohort from 2005 – 2015 – there will be a subsequent shorter review of the main points of interest towards the end of thesis preparation to examine if there have been recent changes. We have requested earlier data to establish cohort stability in 2005.

Please indicate the geographic area for which data is requested
Wales – all Health Boards
Please indicate demographic criteria for the data requested (age, gender, etc.)
18 years and above, all people accessing primary/ secondary/ tertiary care

9b. Will you be providing any other dataset(s) to be incorporated into the SAIL databank?
Yes [☐] No [☒]
If yes:
Provide the name of the dataset(s):
Provide details of the contents of the dataset(s):

9c. Provide an outline of your analysis plan including the anticipated outputs: See attached protocol

9d. Are the results/methods developed likely to have other potential applications?
Yes [☒] No [☐]
If yes, please specify:
This methodology may be used to examine the impact of prescribing within other specialities / morbidities in future.

The results will be shared with Welsh Government organisations e.g., All Wales Medicines Strategy Group as part of a policy development.

10a. Please indicate your plans for publishing the results of your project, e.g.,, target journal or intended recipients of report:
The work will form part of a PhD thesis and will also be used to develop articles for publishing in pain and economics journals e.g.,, European Journal of Pain.

Results will be disseminated to national and international conferences and journals for publishing.

10b. What are the potentially sensitive issues that need to be taken into account when publicising the findings of the project?

Please outline the issues and your proposed solutions:

Issues over prescribing are often deemed sensitive, should they reveal certain patterns that could be attributed to individual prescribers. In this case, however, all data is anonymised. Further, certain aspects e.g.,, Health Board where the prescribing took place, is already in the public domain and therefore, it is not expected that any issues arising from this study will be particularly sensitive. Opiate addiction sometimes manifests certain very apparent signs: dependency, physical withdrawal symptoms, financial problems and behavioural change. Due care and attention will be paid to the presentation of data to ensure that no small cell counts are generated or can be derived from the outputs. This will ensure that any reader of the research could not attempt, in conjunction with other data or observations known to them, to deduce the identity of any individual.

What to do next

Please return your completed form and supporting documents by email to Cynthia McNerney, Information Governance Coordinator g[redacted] Thank you

A.2 TOPAS Project specification

Prerequisite requirements

We have only been given project encrypted LSOA codes, so determination of Health Board area of residence is not possible with the current dataset. Submit an IGRP amendment to obtain unencrypted LSOA code.

Stepwise data processing.

1. **Determine read codes for opiate prescribing**
   - 1a. Produce a list of medication read codes for opiate drugs/ all pain management medications with indication of usage in SAIL by year 2005 to 2015 to provide to Emma for confirmation of project inclusion
   - 1b. Establish a cohort of patients with any prescription of opioids from the list of 1.a
2. **Determine a project cohort**
   - 2a. Import list of cancers from Nottingham to be provided by Emma, for exclusion criteria, and perform any code mapping required to interpret it.
   - 2b. Produce data table of opioid prescribing pattern per patient. To include start opioid prescribing, end of prescribing, data available over the interim period in the study period. Flag up cancer patients (using Nottingham list), other chronic pain patients, and non-chronic pain patients
   - 2c. Establish the inclusion / exclusion criterion from the Opioid prescribed patients that the project wishes to include and exclude (e.g.,, chronic pain vs single Co-codamol prescription for short term recovery, time and data available in the study period)
   - 2d. Finalise the “Opioid users pool” cohort.
3. **Establish non opioid comparator group**
   - 3a. Establish if a cohort of people exist with chronic pain who are not prescribed opioids or very few opioids
   - 3b. Create a comparator group, excluding cancer patients
4. **Create comorbidity and health service utilisation data for the previously defined opioid and non-opioid cohorts**
   - 4a Establish patient profiles with age, gender, long term conditions, regular medications etc., date of death where applicable from GP data. Include information on the completeness of patient’s records in the primary care data during the study period (i.e., periods registered with participating GPS). Should include geographical marker, i.e., Health Board for area comparator. Should include number of Primary Care events.
   - 4b Linkage to PEDW to establish day case and inpatient hospitalisation during the study period, including admission method, dates, diagnoses, operative procedure, length of stay and costing data.

4c Linkage to EDDS data to include all attendances at A&E in the study period, including reason for attendance, dates, injuries, outcomes.

4d Linkage to Outpatient data to include all outpatient attendances during the study period, consultant specialty, clinic, specialty, dates, attendance information

4e Linkage to ADDE mortality data to include date and primary and secondary causes of death where applicable.

A.3 Original study protocol

Trends in Opioid Prescribing and ASsociated resource utilisation in Wales (TOPAS)

Student: Emma Davies

Supervisors: Professor Ceri Phillips, Dr Jaynie Rance, Dr Bernadette Sewell, Professor Roger Knaggs (Nottingham), Professor Damon Berridge

Lay summary of research

Opioids are drugs, derived directly from or related to the naturally occurring alkaloids found in the opium poppy (papaver somniferum). The terms 'opiate' and 'opioid' are often used interchangeably although they technically denote a subtle difference in that opiates are 'naturally occurring' i.e., derived directly from opium and opioids are partially or wholly synthetic, with their chemistry based on the compounds derived from opium. Traditionally, opioids have been used to treat pain following trauma and surgery and also in the management of pain due to cancer and at the end of life.

In the last twenty to thirty years, there has been increasing use of opioids for the long-term treatment of chronic, non-cancer pain (CNCP), arising from conditions such as osteoarthritis, low back pain and fibromyalgia. This is despite the medical evidence being limited to short-term benefits and side effects of these drugs. Much less is known about the effectiveness and safety of opioids when given over longer treatment periods and in high doses for non-cancer pain.

Scientific literature and national media in the United Kingdom have expressed concern about whether the known increase in opioid prescribing will lead to increased incidence of dependence and misuse. Studies from North America suggest that patients taking opioids use more healthcare resources than other patients and may have a higher death rate than non-users.

In Wales, there are similar concerns following several years of increasing numbers of deaths involving opioid medications and a general upwards trend in opioid prescribing. However, to date, there has not been a large-scale, observational study assessing the actual patterns of opioid use in clinical practice over extended periods of time nor if any link exists between the use of these drugs and other health care utilisation.

Insight into the consequences of chronic non-cancer pain, particularly focussed on the use of opioids, has been little studied in the general public or 'patients'. Numerous studies have enquired into clinician's perceptions of chronic pain, how it is best managed and the prescribing and safety of opioid medication within that context. There appears to be less literature examining patients' thoughts on the best ways to manage their pain or if they share similar concerns to practitioners and researchers about the rapid rise of opioids as part of that management.

This study, therefore, aims to describe the use of opioids in all Welsh patients prescribed them and whose data is available via a national repository. The

prescribing patterns and clinical outcomes, including all interactions with health care services across sectors will be evaluated in order to determine if there is an association between opioid use and health care utilisation.

From this, the intention is to establish an economic estimation of the costs of opioid use in chronic, non-cancer pain and which will allow services to develop more meaningful models of care and management to benefit patients in the long-term.

Research Hypotheses

- That opioid utilisation has increased in Wales in the last 10 years and varies between different Health Boards, population demographic and type of prescriber
- That there is association between individual patients' use of opioids and their use of health care resources and that this relationship can be determined by the opioid being used, persistence of use and the doses prescribed

Research Aims

This study aims to:

- Describe the trends of opioid prescribing in the Welsh Primary Care Population, over a 10-year period (2005 – 2015)
- Determine any causal or potential association between opioid use, non-pain morbidities and the utilisation of other health care services, in primary, community or acute care settings
- Develop an economic evaluation that enables the full costs of opioid use in chronic, non-cancer pain to be more accurately determined, in order to inform the development of more effective services for pain management and improved use of medicines

Research objectives

To describe the trends of opioid prescribing

1. Opioid utilisation and prescribing patterns evaluation
    a. To evaluate the prescribing data of opioid prescriptions and to explore geographic (Health Board), patient age and deprivation level variations
    b. To investigate the impact of major clinical guidance and recent legislative changes on opioid prescribing patterns

2. Opioid prescribing persistence in chronic, non-malignant pain management
    a. To determine the persistence of opioid prescribing and assess whether the persistence and pattern of prescribing can be a proxy for measuring adherence, drug diversion and misuse
    b. To determine the potential factors contributing to persistence of long-term opioid prescribing including the nature of CP being treated

3. Clinical outcomes related to long-term opioid utilisation

a. To assess adverse effects which are associated with short-term and long-term opioid use
b. To compare the mortality rate between opioid and non-opioid users in patients with a specific chronic, non-malignant pain condition

To determine associations between opioid use, morbidity and health care utilisation:

4. Association between opioid use and health care utilisation
    a. To assess the frequency of primary and secondary healthcare referral or attendance by patients on long-term opioids therapy compared to the general population (patients not receiving opioids)
    b. To assess if any association is determined by the type of opioid medication (e.g.,, weak or strong opioid) being prescribed, the doses administered or the duration of use

To evaluate the cost of opioid use in chronic, non-cancer pain:

5. Estimation of the 'true cost' of opioid prescribing
    a. To develop economic descriptions of the impact of health care utilisation associated with long-term opioid therapy which may then be used in the development of strategies to change how opioid prescribing is used in CP

Background

Pain is generally defined as 'an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or is described in such terms. (Merskey H, Bogduk N, 1994) Chronic pain (CP) is accepted to be pain that has persisted for longer than three months and can be more accurately described as chronic, non-malignant pain (CNMP) or chronic non-cancer pain (CNCP), which helps to further differentiate it from pain associated with end-of-life morbidities, tumours or chemotherapy.

Chronic pain may result from nociceptive or neuropathic aetiologies and some people will display elements of both. People living with CP will commonly have comorbidities such as sleep disturbance, anxiety and depression in addition to physical debilitation. (Martelli MF et al. 2004) Severe CP also adversely affects employment, relationships and people's general health, for example daily back pain is associated with a higher incidence of coronary events (National Pain Audit, 2012(National Pain Audit Final Report,2012). The complex interplay of bio-psychosocial factors results in CP causing a reduction in the quality of life of sufferers more than almost any other condition (Chief Medical Officer, 2009(READING BETWEEN THE LINES: The annual profile for substance misuse 2014-15, 2015).

The reported prevalence of CP varies considerably depending on the type of pain being recorded and the population being studied. The Chief Medical Officer's report 2008 gave an estimate of 7.8 million people in the United Kingdom being affected by moderate to severe pain of 6 months duration or more. This pertains

to over a third of households having someone in pain at any given time (READING BETWEEN THE LINES: The annual profile for substance misuse 2014-15, 2015). The high economic burden of CP in addition to poor quality of life has resulted in increasing attention being paid to its treatment over the last 10 years.

In Wales as in the rest of the UK, estimates of around 13% of the population are likely affected by chronic pain (Breivik H et al, 2006). The Welsh Government published a commissioning directive in 2008, aimed at improving access to multi-disciplinary, multi-modal pain services the intimation being at that time, that services were developed around the skills and experience of the professionals running the services rather than patient need (Welsh Government, 2008).

The use of opioids to treat pain has been established for thousands of years and commonly accepted for the treatment of cancer and acute pain e.g.,, pain associated with trauma or surgery (Kalso E et al, 2004). Over more recent times, the use of opioids in the treatment of CP has increased. Some attribute the change in attitude to opioids to a sentinel paper by Portenoy and Foley in the late 1980's that appeared to open the door to a more liberal approach to prescribing in non-cancer pain (Portenoy, 1986) despite the available evidence being limited to short-term efficacy and side-effects. It is thought that opioids are likely to have less effect over time periods longer than 12 weeks and beyond certain doses the harms of continuation outweigh any therapeutic benefits (Opioids Aware, 2015).

Concerns over the risk of dependence, tolerance and addiction have been raised (Chou et al, 2009; Franklin, GM, 2014).

Despite this, over the last 10 to 15 year period, Wales has seen an increase in analgesic prescribing, which fits with general trends in the UK, Europe and the United States. ((Zin, Chen, & Knaggs, 2014); (Ruscitto, Smith, & Guthrie, 2014); (Wright, Katz, Abrams, Solomon, & Losina, 2014); (Fredheim, 2010); (Olsen, Daumit, & Ford, 2006) In the UK, a doubling of opioid prescriptions was seen in the five-year period to 2011, (NTA, 2011) Although the exact reasons for this trend have still to be fully elucidated more recent studies have demonstrated the increase to be associated with use in CP. (Zin et al., 2014)

Patient's adherence to opioids, the incidence of adverse-effects, risks of dependence and addiction and the impact on patient's general health are not clearly defined in a Welsh or UK-wide population. The British Pain Society initially published good practice guidelines for prescribing opioids in persistent pain in 2004 (BPS, 2004) and this is now updated to an online, evidence-based resource (Opioids Aware, 2015). The effect in practice of such initiatives is unclear beyond what can be elucidated from prescribing data.

The current study attempts to begin to address the overall use of opioids in the Welsh population and to develop an economic model to examine the impact of existing patterns and potential benefits of future change. The effectiveness and

safety of long-term opioid use in the management of chronic pain will be explored as well as any association with differences in other health care utilisation or clinical morbidity in those receiving opioids for CP compared to those who do not.

Study type
This study is in two parts; firstly, an observational study to analyse opioid utilisation and patient characteristics as well as to assess the association between long-term opioid exposure and clinical outcomes including the use of non-pain related health care services in Wales.

Secondly, the development of an economic evaluation that accounts for all facets of opioid prescribing and which will allow a realistic estimation of cost-benefits of any proposed future changes to prescribing or the allocation of services.

Prescribing trends study
Cross sectional study design: This will be achieved via a quantitative, observational study conducted using a cross-sectional (with repeated cross-sections) and longitudinal cohort study designs, during a ten-year period from 2005 – 2015. Data will be accessed via the Secured Anonymised Information Linkage (SAIL) Databank, which provides hospital episode statistic (HES) data in addition to primary care prescribing and other health care interactions.

All patients aged 18 years or over (adult), at any point in the study period (2005 – 2015) and prescribed any of the identified opioid drugs during that period, will be included in the cross-sectional study. Identification of patients will be solely by the prescription of opioids, using specific drug product codes from the SAIL datasets.

The commonly prescribed opioid or opioid-containing drugs selected as study drugs for this purpose include; codeine phosphate, codeine and paracetamol (co-codamol), dihydrocodeine, dihydrocodeine and paracetamol (co-dydramol), buprenorphine, dextropropoxyphene, dextropropoxyphene and paracetamol (co-proxamol), tramadol, tramadol and paracetamol, morphine, oxycodone, hydromorphone, fentanyl, tapentadol, meptazinol and pethidine. Prescriptions will be identified by read code and then duration data will be calculated. The outcome measures will be summed and repeatedly calculated to generate monthly and annual data.

Included patients' opioid prescription records will be measured repeatedly during the study period (2005 – 2015) and then collated to generate a range of prescribing measures in aggregated time-series and monthly/annual time-series data in order to undertake trend analysis.

Measures on utilisation of study drugs include the number of prescriptions, the strength of dosage form and the cost of opioids described. Costs will be ascribed using data from national tariffs for prescription medication.

In this study, there is no particular selection of comparison and instead the data will be stratified by Health Board. Aggregated utilisation and time-series data will be stratified according to Health Board and demographic of the local population to determine any variation.

Various legislative changes e.g., Controlled drug legislation post-Shipman, change in controlled drug scheduling of tramadol in 2014, introduction of new drug-driving legislation in 2015 will be used as marker points. Any changes in opioid prescribing after those dates may then be attributed to the guidance or legislation changes.

Cohort study design: All patients aged 18 or over (adult) at any point in the study period (2005 – 2015) and with a specified coded chronic pain condition e.g., low back pain will be included in the cohort study. All patients with a cancer diagnosis at any point in their medical history will be excluded from this arm of the study. (Due to the potential problems with coding in primary care in particular, in order to ensure that patients receiving opioids for chronic, non-cancer pain only are included in the cohort study, it will be necessary to identify all patients who have ever received a cancer diagnosis and then remove their data from this section of analysis).

Chronic pain conditions include back pain, chronic low back pain, spinal pain, neck pain, osteoarthritis, inflammatory arthritis (ankylosing spondylitis, psoriatic arthropathy, rheumatoid arthritis), painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia and phantom limb pain. For clinical outcomes, only patients with complete records including hospital episode statistics (HES) will be included in the final analysis.

Adult patients with specific chronic, non-cancer pain conditions will be selected from 2005 at the beginning of the study period and grouped into either non-opioid users (control group), short-term opioid users (<6 months) or long-term opioid users (>6 months).

In order to control confounding for clinical outcomes, the intervention and control groups will be matched by age, gender, Charlson Comorbidity Index (CCI) (Quan, 2011), inclusion day, opioid history (2004-2005) and deprivation score.

Patients will be followed from the date of the first prescription of any of the study drugs – within the study period to six months after the final prescription covering date or the end of the study period. This mirrors the selections of Zin et al and would allow comparison with combined data for Wales and England at a later time (Zin et al., 2014).

Prescribing persistence is defined as, ‘the duration of time from initiation to discontinuation of therapy’ (Cramer et al., 2008). Prescription of study drugs, prescribed dose and duration of prescribing will be analysed for individual

patients. The duration of prescribing will be used to calculate exposure days, prescription covering days and to then estimate the medication possession ratio (MPR). The MPR will be further adjusted by covariates such as socio-demographic characteristics (e.g., age at diagnosis, sex, deprivation scores), smoking and alcohol use, co-morbid conditions, number of drugs prescribed and disease-related pain conditions.

Adult patients with a specified chronic pain indication (low back pain) are included and the corresponding opioid drug utilisation data will be analysed. Evaluating prescribing persistence and medication possession ratio (MPR) will identify patients who have continuous short-term or long-term exposure to any of the study drugs. Patients identified with a specified CP indication but without an opioid prescription will be entered into the control group.

Continuous use is assumed when the gap between each opioid prescription-covering period is less than 30 days. Short-term use refers to the accumulated period of opioid prescription covering less than 180 days (6 months). Long-term use refers to the accumulated prescription period covering more than 180 days (6 months). The intervention (long-term users) and control groups will be selected by 1:1 matching in age, gender, CCI, inclusion day, opioid use history (2004 – 2005) and deprivation score.

Prescription data for the study opioid drugs for individual patients will be collected; number of items and where possible, dose data and duration of prescribing will be used to assess prescribing persistence. The medication possession ratio (MPR)(calculated from number of days of medication supplied within the refill period) for different opioids will be compared between different types of CP.

Clinical outcomes will be analysed using read codes for the most common adverse effects (ADE) of opioids (constipation, nausea, dizziness and drowsiness and vomiting) will be used to search the records of all adult patients with a CP indication and opioid prescription. Proxy measures such as anti-emetic and laxative prescriptions will be evaluated. Comparison will be made of ADEs and their frequency between long-term and short-term opioid users and further comparison made between those and the control group in order to determine ADE rates between the groups and if an association can be made between opioid use and duration of use.

Mortality rates of long-term and short-term opioid users will be calculated and compared to each other and to the mortality rate within the control group.

Association between opioid use, morbidity and health care utilisation
Study design: Health care utilisation in all sectors including those related to managing pain or opioid related outcomes will be captured using ICD-10 and OPCS-4 coding in according with the data recording methods for the Patient Episode Database for Wales (PEDW), which collects hospital data. Long-term

ADE such as endocrine, immune dysfunction, sexual dysfunction and infertility will be examined, by proxy measures if necessary, such as GP and outpatient attendances. Time to events will also be measured. Data will be grouped according to long-term or short-term opioid use and compared to the control group of patients not receiving opioid prescriptions.

Health care utilisation data in patients receiving opioid prescriptions will be further analysed by categorising into 'weak' and 'strong' opioids as per the World Health Organisation (WHO) analgesic ladder {Anonymous:wj} and then further by dose banding of <20mg, 20-49mg, 50-99mg, 100-199mg and >200mg daily MEQ and as described in previous work (Dunn, Saunders, & Rutter, 2010, Gomes, Mamdani, Dhalla, Paterson, & Juurlink, 2011). Duration of prescribing will be a secondary measure to analyse the association between prescribed opioid dose and healthcare interactions.

To Estimate the cost of opioid use in chronic, non-cancer pain:

1. Estimation of the cost of opioid prescribing
    a. To develop economic descriptions of the impact of health care utilisation associated with long-term opioid therapy which may then be used in the development of strategies to change how opioid prescribing is used in CP

Sample size / Power calculations

It has been estimated that 13% of the UK population suffer with moderate to severe pain (Breivik, 2006), which, equates to 400,000 people in Wales, a country with a population of around 3 million (Statistics Wales, 2015). In the European Union (EU), 13% of patients with persistent pain appear to be prescribed weak opioids and 3% strong opioids (Langley, 2011).

Using the estimated prevalence of chronic pain above, this suggests 52000 patients receive prescriptions for weak opioids and 12000 patients' strong opioids in Wales. However, there has been a marked increase in prescribing of opioid analgesics within primary care in Wales from 1 million items in 2007 to 1.4million items in 2013, an increase of nearly 40%, meaning that these figures could be an underestimate.

The SAIL database in Wales as a whole represents over 70% of Primary Care Practices (General Practitioners). Therefore, the Law of Large Numbers and Central Limit Theorem dictate that it should be expected to estimate these effects accurately. In fact, the Law of Truly Large Numbers may be used even to detect differences in rare events, if it is found to be relevant to the study.

In clinical trials of short duration, over half (51%) of patients taking opioids within clinical trials experience at least one treatment emergent adverse effect. (Moore, 2005) Recent data from the United States (US) suggest doses of morphine 200mg (or equivalent dose of an alternative opioid), were associated with a nearly 3-fold increase in the risk of opioid-related mortality. (Gomes, 2011)

Since long-term opioid exposure information is limited in Wales, there are currently no estimates with which to determine power-based sample sizes for detecting the association between long-term opioid exposure and clinical outcomes. Similarly, no estimates can be made for power-based sample sizes for quantifying any apparent causal relationship.

Data / Statistical Analysis

Data management
Records with missing dates of birth, diagnosis and drug, which consequently, are unable to identify age, disease conditions and drug utilisation, will be excluded from the analysis. However, as appropriate, then a progressive procedure will be in place to either incorporate or exclude missing data.

Missing data will be included in the sensitivity analysis; firstly, it will be flagged and then used to compare analyses in which missing data is dropped with analyses relying on multiple imputations. This will enable the establishment of randomness and leverage of any missing data.

All datasets will be stored on SAIL use authenticated, password protected servers. Although access can be gained remotely, data extraction from the server is not possible without written authority from SAIL. The database mainframe is situated in a locked and highly secured building. Initial data extraction can only be performed by a trained coder with the appropriate level of security clearance from SAIL. All data is anonymised.

Extracted data will be double encrypted before being made available to the researcher in order to maintain its security. Individual SAIL records will not be divulged outside of the research group (researcher, supervisors and informatics support).

Information processing and data analysis will be performed on mainstream applications such as IBM SPSS©, in addition to specialised statistical and econometric packages like STATA 14 (Stats Corp LP, 2014. USA).

Statistical analysis
Baseline descriptive analysis will be undertaken for all variables in the study, in order to ensure data and variables are included and analysed appropriately. Simple statistical analysis methods (e.g., Analysis of Variance (ANOVA)) will be used to compare average drug utilisation across different groups. Linear trend analysis will be used on time-series data before further time-series analysis is undertaken.

For the longitudinal data, either static (cross-sectional modelling for correlation and treatment effects, including generalised linear-regression modelling) or dynamic (repeated cross-sectional and longitudinal methods including generalised estimating equations), seemingly unrelated regression and panel

data methods will be used. The Cox proportional hazard model will be used to compare outcome events and time to events between groups and the results reported as hazard ratio (HR) and 95% confidence interval (95% CI).

Patient or User-group involvement

This study evaluates an established medical intervention requiring no patient user group involvement in this instance.

Predictable limitations of the Prescribing Trends study design, data sources and analytic methods

- The study uses secondary data where the investigator has not witnessed the care provided or collected the data directly. Therefore, an assumption is made that the data is accurately recorded and the interventions have actually taken place as described.
- Measuring opioid use on the basis of prescriptions issued may not reflect the actual utilisation as the drugs may not have been dispensed by a pharmacy or taken by the patient.
- Measuring medication adherence using prescription issue also means it is not possible to determine if the patient actually had the prescription dispensed or consumed the dispensed medication themselves. Some people may order a prescription but not get it refilled. Some people may get prescriptions dispensed more often than they take the medication, or they may store medication for future use or in some cases, give or sell it to others.

Dissemination

The findings from this study will be prepared for publication in refereed international journals. The findings will also be communicated at conferences, seminars, research workshops and meetings.

With the extensive links to patients and professional stakeholder that Swansea University has, the results will also be made available to them for comment. This work contributes to a programme of research based in the Swansea Centre for Health Economics that focuses on using large patient databases to assess drug utilisation, prescribing patterns, medicines adherence, clinical outcomes and economic impact related to the studied drugs and diseases. Therefore, this work will also contribute to comparative analysis of the methods and results across disease types and patient groups, and dissemination is likely to include this aspect of the work.

References

- Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2012). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. European Journal of Pain, 10(4), 287–287.
- British Pain Society. Opioids for persistent pain: Good practice. 2004
- Chief Medical Officer. Pain: Breaking through the barrier. Department of Health, 2009; 1 – 8.
- Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic non-cancer pain: Findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline. Journal of Pain. 2009; 10 (2); 147 – 59
- Cramer, J. A., Roy, A., Burrell, A., Fairchild, C. J., Fuldeore, M. J., Ollendorf, D. A., & Wong, P. K. (2008). Medication Compliance and Persistence: Terminology and Definitions. Value in Health, 11(1), 44–47. http://doi.org/10.1111/j.1524-4733.2007.00213.x
- Dunn, K. M., Saunders, K. W., & Rutter, C. M. (2010). Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. Annals of Internal …. http://doi.org/10.1059/0003-4819-152-2-201001190-00006

- Fairman, K., & Motheral, B. Evaluating Medication Adherence: which measure is right for your program? Journal of Managed Care Pharmacy, 2000. 6 (6), 499–506.
- Franklin GM. Opioids for chronic non-cancer pain: A position statement of the American Academy of Neurology. Neurology. 2014; 83 (September); 1277 – 1284.
- Fredheim, O. M. S., Skurtveit, S., Breivik, H., & Borchgrevink, P. C. (2010). Increasing use of opioids from 2004 to 2007 – Pharmacoepidemiological data from a complete national prescription database in Norway. European Journal of Pain, 14(3), 289–294. http://doi.org/10.1016/j.ejpain.2009.05.006
- Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side-effects. Canadian Medical Association Journal. 2006; 174 (11): 1589 – 94.
- Gomes, T., Mamdani, M. M., Dhalla, I. A., Paterson, J. M., & Juurlink, D. N. (2011). Opioid Dose and Drug-Related Mortality in Patients With Nonmalignant Pain. Archives of …, 171(7), 686–691. http://doi.org/10.1001/archinternmed.2011.117
- https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/clinical-use-of-opioids/effectiveness-for-long-term-pain (Accessed November 2015)
- Kalso, E, Edwards JE, Moore RA, McQuay HJ. Opioids in non-cancer pain: systematic review of efficacy and safety. Pain. 2004; 112 (3); 372 – 80)
- Langley PC. The prevalence, correlates and treatment of pain in the European Union. Current Medical Research and Opinion. 2011; 27 (2): 463 - 80
- Martelli MF, Zasler ND, Bender MC, Nicholson K. Psychological, neuropsychological and medical considerations in assessment and management of pain. Journal of Head Trauma Rehabilitation. 2004; 19 (1); 10 – 28.
- Merskey H, Bogduk N. Classification of chronic pain – descriptions of chronic pain syndromes and definitions of pain terms. 2 ed. Seattle: International Association for Study of Pain; 1994.
- Moore RA, McQuay HJ. Prevalence of opioid adverse effects in chronic, non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Research and Therapy. 2005; 7 (5): R1046 – 51.
- National Pain AuditFinal Report. (2012). National Pain AuditFinal Report, 1–66.
- Olsen, Y., Daumit, G. L., & Ford, D. E. (2006). Opioid Prescriptions by U.S. Primary Care Physicians From 1992 to 2001. The Journal of Pain, 7(4), 225–235. http://doi.org/10.1016/j.jpain.2005.11.006
- Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain. 1986; 25 (2); 171 - 86
- Quan, H., Li, B., Couris, C. M., Fushimi, K., Graham, P., Hider, P., et al. (2011). Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. American Journal of Epidemiology, 173(6), 676–682. http://doi.org/10.1093/aje/kwq433
- READING BETWEEN THE LINES: The annual profile for substance misuse 2014-15. (2015). READING BETWEEN THE LINES: The annual profile for substance misuse 2014-15, 1–86.
- Ruscitto, A., Smith, B. H., & Guthrie, B. (2014). Changes in opioid and other analgesic use 1995-2010: Repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. European Journal of Pain, 19(1), 59–66. http://doi.org/10.1002/ejp.520
- Welsh Assembly Government. Designed for people with chronic conditions; Service development and commissioning directives; Chronic non-malignant pain. 2008, 1 – 46.
- Welsh Government & Statistics Wales. (2015). 2014 Mid-year Population Estimates for Wales (No. SB 34/2015) (1–8). Cardiff.
- Wright, E. A., Katz, J. N., Abrams, S., Solomon, D. H., & Losina, E. (2014). Trends in Prescription of Opioids From 2003–2009 in Persons with Knee Osteoarthritis. Arthritis Care & Research, 66(10), 1489–1495. http://doi.org/10.1002/acr.22360
- Zin, C. S., Chen, L. C., & Knaggs, R. D. (2014). Changes in trends and pattern of strong opioid prescribing in primary care. European Journal of Pain, 18(9), 1343–1351. http://doi.org/10.1002/j.1532-2149.2014.496.

A.4 Read codes for opioid analgesics

Table A.1: Read codes for weak opioid analgesics including the original list shared from Nottingham University

Read code (Version 3)	Term ID	Term details
Dextropropoxyphene		
dia7.	y029g	Co-proxamol 32.5mg/325mg tablet
diax.	y07bS	Co-proxamol 32.5mg/325mg/5mL s/f suspension
diaw.	y029s	Cosalgesic tablet
dj61.	y02BC	Dextropropoxyphene hydrochloride 65mg capsule
diad.	y029i	Distalgesic tablet
dibh.	y00IU	Paxalgesic tablet
Dipipanone		
x01KW	y047z	Dipipanone
dj92.	y02Bc	Dipipanone+cyclizine 10mg/30mg tablet
dj91.	y02Bb	Diconal tablet
Buprenorphine		
dj3p.	y0GpG	Buprenorphine 10micrograms/hour patch
dj3q.	y0GpH	Buprenorphine 20micrograms/hour patch
dj3o.	y0GpF	Buprenorphine 5micrograms/hour patch
dj3B.	y0GpK	BuTrans 10micrograms/hour patch
dj3C.	y0GpL	BuTrans 20micrograms/hour patch
dj3A.	y0GpJ	BuTrans 5micrograms/hour patch
Codeine		
dia1.	y00I5	Aspirin/paracetamol/codeine tablets
x00et	y03SK	Aspirin+codeine 300mg/8mg tablet
diaq.	y029o	Co-codamol 8mg/500mg capsule
dia3.	y029c	Co-codamol 8mg/500mg dispersible tablet
diap.	y029n	Co-codamol 8mg/500mg effervescent tablet
dia2.	y029b	Co-codamol 8mg/500mg tablet
dia5.	y029e	Co-codaprin 8mg/500mg dispersible tablet
dia4.	y029d	Co-codaprin 8mg/500mg tablet
diaO.	y0EdF	Co-codaprin 8mg/500mg dispersible tablet
dj41.	y02Ay	Codeine phosphate 15mg tablet
cg11.	y01vd	Codeine phosphate 15mg/5mL linctus
cg12.	y0AVG	Codeine phosphate 15mg/5mL s/f linctus
dj44.	y02B1	Codeine phosphate 25mg/5mL syrup
dj42.	y02Az	Codeine phosphate 30mg tablet
dj43.	y02B0	Codeine phosphate 60mg tablet
dj45.	y02B2	Codeine phosphate 60mg/1mL injection
dica.	yz4v2	CODIPAR 15mg/500mg effervescent tablets
diaT.	y0F5Q	Codipar Caplet
diaP.	y0EdI	Codis 500 dispersible tablet
diab.	y00I8	Codis dispersible tablet
cg14.	y01vg	Galcodine 15mg/5mL s/f linctus
j28O.	y0844	Ibuprofen+codeine phosphate 200mg/12.5mg tablet
j28V.	y09u6	Ibuprofen+codeine phosphate 200mg/12.8mg tablet
j28z.	y02xj	Ibuprofen+codeine phosphate 300mg/20mg m/r tablet
dicN.	y0Fw0	Kapake 30/500 effervescent tablet
diao.	y0CrA	Kapake capsule
diaL.	y0CYe	Kapake Insts 1000mg/60mg/sachet powder
diaJ.	y0CRd	Kapake Insts 500mg/30mg/sachet powder
diam.	y01Ez	Kapake tablet
dib3.	y00IH	Medocodeine tablet
dibW.	y0DDg	Medocodene 30/500 capsule
dicR.	y0Gom	Medocodene 30/500 effervescent tablet
dl13.	y02CL	Migraleve yellow tablet
dl1a.	y00JK	Migraleve yellow tablets x48
j28I.	y0845	Nurofen Plus tablet
dib9.	y00IN	Panadeine Forte tablet
diba.	y00IO	Panadeine soluble tablet
dib8.	y00IM	Panadeine tablet
dibN.	y09zp	Panadol Ultra tablet
diaK.	y0CYd	Paracetamol+codeine phosphate 1000mg/60mg/sachet powder
dia3.	y08Gi	Paracetamol+codeine phosphate 500mg/8mg dispersible tablet
dia2.	y08Gh	Paracetamol+codeine phosphate 500mg/8mg tablet

dibQ.	y0CJ1	Paracetamol+codeine phosphate 500mg/12.8mg tablet
dibM.	y09zo	Paracetamol+codeine phosphate 500mg/13.5mg tablet
dicv.	yz4v3	PARACETAMOL+CODEINE PHOSPHATE 500mg/15mg effervescent tablet
diaU.	y0F5P	Paracetamol+codeine phosphate 500mg/15mg tablet
dibD.	y029w	Paracetamol+codeine phosphate 500mg/30mg capsule
dibB.	y029u	Paracetamol+codeine phosphate 500mg/30mg effervescent tablet
dian.	y01M5	Paracetamol+codeine phosphate 500mg/30mg tablet
diaI.	y0CRc	Paracetamol+codeine phosphate 500mg/30mg/sachet powder
diar.	y09aF	Paracodol capsule
dibb.	y029v	Paracodol soluble tablet
dibc.	y00IP	Paradeine tablet
dibe.	y00IR	Parake tablet
dibo.	y00Ia	Solpadeine Forte dispersible tablet
dibR.	y0CJ2	Solpadeine Max tablet
j2pT.	y0H2p	Solpadeine Migraine Ibuprofen & Codeine tablet
x04uo	y0Fj8	Solpadeine Plus capsule
dibn.	y0FjA	Solpadeine Plus Soluble effervescent tablet
dibz.	y02A4	Solpadol Caplet
dibS.	y0CLZ	Solpadol capsule
dibu.	y02A1	Solpadol effervescent tablet
dibp.	y00Ib	Syndol tablet
dibt.	y02A0	Tylex capsule
dibG.	y08J2	Tylex Effervescent soluble tablet
dicM.	y0Foo	Ultramol capsule
dicL.	y0Fon	Ultramol tablet
dibX.	y0DWj	Ultramol soluble tablet
dibs.	y00Ie	Veganin tablet
dic3.	y0DZy	Zapain Caplet
dic4.	y0DZz	Zapain capsule
Dihydrocodeine		
dj85.	y00J4	DF118 10mg/5mL elixir
dj84.	y00J3	DF118 30mg tablet
dj86.	y00J5	DF118 50mg/1mL injection
dj8d.	y01Ic	DF118 Forte 40mg tablet
dj8a.	y02BX	DHC Continus 120mg m/r tablet
dj87.	y02BU	DHC Continus 60mg m/r tablet
dj89.	y02BW	DHC Continus 90mg m/r tablet
dj8..	y02BQ	Dihydrocodeine tartrate
dj82.	y02BS	Dihydrocodeine tartrate 10mg/5mL elixir
dj8c.	y02BZ	Dihydrocodeine tartrate 120mg m/r tablet
dj81.	y02BR	Dihydrocodeine tartrate 30mg tablet
dj8e.	y01Id	Dihydrocodeine tartrate 40mg tablet
dj83.	y02BT	Dihydrocodeine tartrate 50mg/1mL injection
dj88.	y02BV	Dihydrocodeine tartrate 60mg m/r tablet
dj8b.	y02BY	Dihydrocodeine tartrate 90mg m/r tablet
dia6.	y029f	Co-dydramol 10mg/500mg tablet
dicy.	y0Gpm	Paracetamol 500mg / dihydrocodeine tartrate 7.46mg effervescent tablet
dibH.	y09nZ	Paracetamol+dihydrocodeine tartrate 250mg/20mg effervescent tablet
dibI.	y09na	Paracetamol+dihydrocodeine tartrate 250mg/30mg effervescent tablet
dibE.	y029x	Paracetamol+dihydrocodeine tartrate 500mg/20mg tablet
dibF.	y029y	Paracetamol+dihydrocodeine tartrate 500mg/30mg tablet
dibf.	y00IS	Paramol 10/500mg tablet
dicS.	y0GpQ	Paramol Soluble tablet
dibx.	y01Aw	Paramol tablet
dibK.	y09ne	Remedeine effervescent tablet
dibJ.	y09nc	Remedeine Forte effervescent tablet
dibw.	y02A3	Remedeine Forte tablet
dibv.	y02A2	Remedeine tablet
Tramadol		
djAj.	yz5EN	ACEON 100mg m/r tablets
djAk.	yz5EO	ACEON 150mg m/r tablets
djAl.	yz5EP	ACEON 200mg m/r tablets
djiW.	y0D7m	Dromadol SR 100mg m/r tablet
djiX.	y0D7n	Dromadol SR 150mg m/r tablet

djiY.	y0D7o	Dromadol SR 200mg m/r tablet
djiZ.	y0D7q	Dromadol SR 75mg m/r tablet
djia.	y0DQK	Dromadol XL 150mg m/r tablet
djib.	y0DQL	Dromadol XL 200mg m/r tablet
djic.	y0DQM	Dromadol XL 300mg m/r tablet
djid.	y0DQN	Dromadol XL 400mg m/r tablet
djif.	y0GZd	Larapam SR 100mg m/r tablet
djig.	y0GZe	Larapam SR 150mg m/r tablet
djih.	y0GZf	Larapam SR 200mg m/r tablet
djA1.	y0H8q	MABRON 100mg m/r tablets
djA2.	y0H8r	MABRON 150mg m/r tablets
djA3.	y0H8s	MABRON 200mg m/r tablets
djAf.	yz4v4	MAROL 100mg m/r tablets
djAg.	yz4v5	MAROL 150mg m/r tablets
djAh.	yz4v6	MAROL 200mg m/r tablets
djAc.	yz3FD	MAXITRAM SR 100mg m/r capsules
djAd.	yz3FE	MAXITRAM SR 150mg m/r capsules
djAe.	yz3FF	MAXITRAM SR 200mg m/r capsules
djAb.	yz3FC	MAXITRAM SR 50mg m/r capsules
djA7.	y0IFm	NOBLIGAN RETARD 100mg m/r tablets
djA8.	y0JHo	OLDARAM 100mg m/r tablets
djA9.	y0JHp	OLDARAM 150mg m/r tablets
djAa.	y0JHq	OLDARAM 200mg m/r tablets
dicz.	y0Fyn	Paracetamol 325mg / tramadol hydrochloride 37.5mg tablet
x05sn	y0Fym	Paracetamol+tramadol
dicx.	yz4ki	PARACETAMOL+TRAMADOL HCL 325mg/37.5mg effervescent tablets
djAm.	yz7Ci	TILODOL SR 100mg m/r tablets
djAn.	yz7Cj	TILODOL SR 150mg m/r tablets
djAo.	yz7Ck	TILODOL SR 200mg m/r tablets
djim.	y0HR3	TRADOREC XL 100mg m/r tablets
djin.	y0HR4	TRADOREC XL 200mg m/r tablets
djio.	y0HR5	TRADOREC XL 300mg m/r tablets
dicY.	yz4kf	TRAMACET 325mg/37.5mg effervescent tablets
dicO.	y0Fyo	Tramacet 325mg/37.5mg tablet
dicO.	y0Fyo	Tramacet 325mg/37.5mg tablet
djAi.	yz53f	TRAMADOL 100mg/1mL oral drops solution
djiG.	y0AZ4	Tramadol hydrochloride 100mg m/r capsule
dji5.	y08O3	Tramadol hydrochloride 100mg m/r tablet
dji1.	y01LN	Tramadol hydrochloride 100mg/2mL injection
djiP.	y0CE7	Tramadol hydrochloride 100mg/sachet powder
djiH.	y0AZ5	Tramadol hydrochloride 150mg m/r capsule
dji6.	y08O4	Tramadol hydrochloride 150mg m/r tablet
djiI.	y0AZ6	Tramadol hydrochloride 200mg m/r capsule
dji7.	y08O5	Tramadol hydrochloride 200mg m/r tablet
djiy.	y0Cuo	Tramadol hydrochloride 300mg m/r tablet
djiz.	y0Cup	Tramadol hydrochloride 400mg m/r tablet
dji2.	y01LO	Tramadol hydrochloride 50mg capsule
djiF.	y0AZ3	Tramadol hydrochloride 50mg m/r capsule
djiv.	y0Hvm	TRAMADOL HYDROCHLORIDE 50mg m/r tablets
djiw.	y0Fh8	Tramadol hydrochloride 50mg oro-dispersible tablet
djiC.	y09uV	Tramadol hydrochloride 50mg soluble tablet
djiO.	y0CE6	Tramadol hydrochloride 50mg/sachet powder
djix.	y0D7p	Tramadol hydrochloride 75mg m/r tablet
djiB.	y09kU	Tramake 50mg capsule
djiR.	y0CE9	Tramake Insts 100mg/sachet powder
djiQ.	y0CE8	Tramake Insts 50mg/sachet powder
djiq.	y0Het	TRAMQUEL SR 100mg m/r capsules
djir.	y0Heu	TRAMQUEL SR 150mg m/r capsules
djis.	y0Hev	TRAMQUEL SR 200mg m/r capsules
djip.	y0Hes	TRAMQUEL SR 50mg m/r capsules
djiN.	y0C8U	Zamadol 100mg/2mL injection
djii.	y0Gop	Zamadol 24hr 150mg m/r tablet
djij.	y0Goq	Zamadol 24hr 200mg m/r tablet
djik.	y0Gor	Zamadol 24hr 300mg m/r tablet
djil.	y0Gos	Zamadol 24hr 400mg m/r tablet
djiE.	y09xP	Zamadol 50mg capsule
djie.	y0Fh9	Zamadol Melt 50mg oro-dispersible tablet

djiK.	y0AZ8	Zamadol SR 100mg m/r capsule
djiL.	y0AZ9	Zamadol SR 150mg m/r capsule
djiM.	y0AZA	Zamadol SR 200mg m/r capsule
djiJ.	y0AZ7	Zamadol SR 50mg m/r capsule
djA4.	y0IC3	ZERIDAME SR 100mg m/r tablets
djA5.	y0IC4	ZERIDAME SR 150mg m/r tablets
djA6.	y0IC5	ZERIDAME SR 200mg m/r tablets
dji3.	y01LP	Zydol 100mg/2mL injection
dji4.	y01LQ	Zydol 50mg capsule
djiD.	y09uW	Zydol Soluble 50mg tablet
dji8.	y08O6	Zydol SR 100mg m/r tablet
dji9.	y08O7	Zydol SR 150mg m/r tablet
djiA.	y08O8	Zydol SR 200mg m/r tablet
djit.	y0Hvl	ZYDOL SR 50mg m/r tablets
djiS.	y0Cum	Zydol XL 150mg m/r tablet
djiT.	y0Cun	Zydol XL 200mg m/r tablet
djiU.	y0Cuq	Zydol XL 300mg m/r tablet
djiV.	y0Cur	Zydol XL 400mg m/r tablet
Meptazinol		
o443.	y03J4	Meptazinol 200mg tablet
o441.	y03J2	Meptid 200mg tablet
djb1.	y00JC	Meptid [analg] 200mg tablets
o44z.	y03J5	Meptazinol 100mg/1mL injection
o442.	y03J3	Meptid 100mg/1mL injection
djb2.	y00JD	Meptid [analg] 100mg/1mL injection
Paracetamol and Pentazocine		
diav.	y029r	Paracetamol+pentazocine 500mg/15mg tablet
diah.	y029l	Fortagesic tablet

Table A.2: Read codes for strong opioid analgesics including the original list shared from Nottingham University

Read code (version 3)	Term ID	Term details
Fentanyl		
o4d7.	y0JGc	ABSTRAL 100micrograms sublingual tablets
o4d9.	y0JGe	ABSTRAL 200micrograms sublingual tablets
o4db.	y0JGg	ABSTRAL 300micrograms sublingual tablets
o4dd.	y0JGi	ABSTRAL 400micrograms sublingual tablets
o4df.	y0JGk	ABSTRAL 600micrograms sublingual tablets
o4dh.	y0JGm	ABSTRAL 800micrograms sublingual tablets
o42G.	y0DlA	Actiq 1200micrograms lozenge
o42H.	y0DlB	Actiq 1600micrograms lozenge
o42C.	y0Dl6	Actiq 200micrograms lozenge
o42D.	y0Dl7	Actiq 400micrograms lozenge
o42E.	y0Dl8	Actiq 600micrograms lozenge
o42F.	y0Dl9	Actiq 800micrograms lozenge
o4dG.	yz7SO	BREAKYL 200micrograms buccal film
o4dI.	yz7SQ	BREAKYL 400micrograms buccal film
o4dK.	yz7SS	BREAKYL 800micrograms buccal film
o42B.	y07tK	Durogesic 100micrograms/hour patch
o428.	y07tH	Durogesic 25micrograms/hour patch
o429.	y07tI	Durogesic 50micrograms/hour patch
o42A.	y07tJ	Durogesic 75micrograms/hour patch
o42L.	y0GXC	Durogesic DTrans 100micrograms/hour patch
o42Q.	y0Guy	Durogesic DTrans 12micrograms/hour patch
o42I.	y0GXB	Durogesic DTrans 25micrograms/hour patch
o42J.	y0GXA	Durogesic DTrans 50micrograms/hour patch
o42K.	y0GX9	Durogesic DTrans 75micrograms/hour patch
o42l.	y0JGR	EFFENTORA 100micrograms buccal tablets
o42n.	y0JGT	EFFENTORA 200micrograms buccal tablets
o4d1.	y0JGW	EFFENTORA 400micrograms buccal tablets
o4d3.	y0JGY	EFFENTORA 600micrograms buccal tablets
o4d5.	y0JGa	EFFENTORA 800micrograms buccal tablets
o4dF.	yz5bd	FENCINO 100micrograms/hr patches
o4dB.	yz5bZ	FENCINO 12micrograms/hr patches
o4dC.	yz5ba	FENCINO 25micrograms/hr patches
o4dD.	yz5bb	FENCINO 50micrograms/hr patches
o4dE.	yz5bc	FENCINO 75micrograms/hr patches

o42h.	y0IND	FENTALIS RESERVOIR 100micrograms/hr patches
o42i.	y0IVN	FENTALIS RESERVOIR 25micrograms/hr patches
o42j.	y0IVO	FENTALIS RESERVOIR 50micrograms/hr patches
o42k.	y0IVP	FENTALIS RESERVOIR 75micrograms/hr patches
o42z.	y018r	Fentanyl 100micrograms injection
o42m.		FENTANYL 100mcg buccal tablets
o4dv.	yz3Qs	FENTANYL 100micrograms nasal spray
o4d8.	y0JGd	FENTANYL 100micrograms sublingual tablets
o42x.	y03Iz	Fentanyl 100micrograms/2mL injection
o427.	y07tG	Fentanyl 100micrograms/hour patch
o42r.	y0Dl4	Fentanyl 1200micrograms lozenge
o42R.	y0Gux	Fentanyl 12micrograms/hour patch
o4dP.	yz7UP	FENTANYL 133micrograms sublingual tablets
o42q.	y0Dl5	Fentanyl 1600micrograms lozenge
o4dH.	yz7SP	FENTANYL 200micrograms buccal film
o42o.	y0JGU	FENTANYL 200micrograms buccal tablets
o42v.	y0Dl0	Fentanyl 200micrograms lozenge
o4dx.	yz3Qu	FENTANYL 200micrograms nasal spray
o4da.	y0JGf	FENTANYL 200micrograms sublingual tablets
o424.	y07tC	Fentanyl 25micrograms/hour patch
o4dR.	yz7UR	FENTANYL 267micrograms sublingual tablets
o4dc.	y0JGh	FENTANYL 300micrograms sublingual tablets
o4e3.	yz7WL	FENTANYL 37.5micrograms/hour transdermal patches
o4dJ.	yz7SR	FENTANYL 400micrograms buccal film
o4d2.	y0JGX	FENTANYL 400micrograms buccal tablets
o42u.	y0Dl1	Fentanyl 400micrograms lozenge
o4dA.	yz4jp	FENTANYL 400micrograms nasal spray
o4de.	y0JGj	FENTANYL 400micrograms sublingual tablets
o42y.	y03J0	Fentanyl 500micrograms/10mL injection
o4dt.	yz3Qq	FENTANYL 50micrograms nasal spray
o425.	y07tD	Fentanyl 50micrograms/hour patch
o4dU.	yz7UU	FENTANYL 533micrograms sublingual tablets
o4d4.	y0JGZ	FENTANYL 600micrograms buccal tablets
o42t.	y0Dl2	Fentanyl 600micrograms lozenge
o4dg.	y0JGl	FENTANYL 600micrograms sublingual tablets
o4dN.	yz7UN	FENTANYL 67micrograms sublingual tablets
o426.	y07tF	Fentanyl 75micrograms/hour patch
o4dL.	yz7ST	FENTANYL 800micrograms buccal film
o4d6.	y0JGb	FENTANYL 800micrograms buccal tablets
o42s.	y0Dl3	Fentanyl 800micrograms lozenge
o4di.	y0JGn	FENTANYL 800micrograms sublingual tablets
o4du.	yz3Qr	INSTANYL 100micrograms nasal spray
o4dw.	yz3Qt	INSTANYL 200micrograms nasal spray
o4ds.	yz3Qp	INSTANYL 50micrograms nasal spray
o42W.	y0HUw	MATRIFEN 100micrograms/hr patches
o42S.	y0HUs	MATRIFEN 12micrograms/hr patches
o42T.	y0HUt	MATRIFEN 25micrograms/hr patches
o42U.	y0HUu	MATRIFEN 50micrograms/hr patches
o42V.	y0HUv	MATRIFEN 75micrograms/hr patches
o42b.	y0IGc	MEZOLAR MATRIX 100micrograms/hour patches
o42X.	y0IGY	MEZOLAR MATRIX 12micrograms/hour patches
o42Y.	y0IGZ	MEZOLAR MATRIX 25micrograms/hour patches
o4e2.	yz7WK	MEZOLAR MATRIX 37.5micrograms/hour patches
o42Z.	y0IGa	MEZOLAR MATRIX 50micrograms/hour patches
o42a.	y0IGb	MEZOLAR MATRIX 75micrograms/hour patches
o4e1.	yz7WJ	OPIODUR 100micrograms/hour transdermal patches
o4dW.	yz7WE	OPIODUR 12micrograms/hour transdermal patches
o4dX.	yz7WF	OPIODUR 25micrograms/hour transdermal patches
o4dY.	yz7WG	OPIODUR 50micrograms/hour transdermal patches
o4dZ.	yz7WH	OPIODUR 75micrograms/hour transdermal patches
o42g.	y0IK1	OSMACH 100micrograms/hour patches
o42d.	y0IJy	OSMACH 25micrograms/hour patches
o42e.	y0IJz	OSMACH 50micrograms/hour patches
o42f.	y0IK0	OSMACH 75micrograms/hour patches
o4dm.	y0JI9	OSMANIL 100micrograms/hr patches
o4dr.	yz3Qo	OSMANIL 12micrograms/hr patches
o4dj.	y0JI6	OSMANIL 25micrograms/hr patches
o4dk.	y0JI7	OSMANIL 50micrograms/hr patches

o4dl.	y0JI8	OSMANIL 75micrograms/hr patches
o4dy.	yz4jq	PECFENT 100micrograms nasal spray
o4dz.	yz4jr	PECFENT 400micrograms nasal spray
o4dO.	yz7UO	RECIVIT 133micrograms sublingual tablets
o4dQ.	yz7UQ	RECIVIT 267micrograms sublingual tablets
o4dS.	yz7US	RECIVIT 400micrograms sublingual tablets
o4dT.	yz7UT	RECIVIT 533micrograms sublingual tablets
o4dM.	yz7UM	RECIVIT 67micrograms sublingual tablets
o4dV.	yz7UV	RECIVIT 800micrograms sublingual tablets
o421.	y03Iv	Sublimaze 100micrograms/2mL injection
o422.	y03Iw	Sublimaze 500micrograms/10mL injection
o42P.	y0Gmv	Tilofyl 100micrograms/hour patch
o42M.	y0Gms	Tilofyl 25micrograms/hour patch
o42N.	y0Gmt	Tilofyl 50micrograms/hour patch
o42O.	y0Gmu	Tilofyl 75micrograms/hour patch
o4dq.	yz3Cf	VICTANYL 100micrograms/hour patches
o4dn.	yz3Cc	VICTANYL 25micrograms/hour patches
o4do.	yz3Cd	VICTANYL 50micrograms/hour patches
o4dp.	yz3Ce	VICTANYL 75micrograms/hour patches
o4e8.	yz83K	YEMEX 100micrograms/hour transdermal patches
o4e4.	yz83G	YEMEX 12micrograms/hour transdermal patches
o4e5.	yz83H	YEMEX 25micrograms/hour transdermal patches
o4e6.	yz83I	YEMEX 50micrograms/hour transdermal patches
o4e7.	yz83J	YEMEX 75micrograms/hour transdermal patches
Pentazocine		
djf7.	y02Bv	Fortral 25mg tablet
djf8.	y02Bw	Fortral 30mg/1mL injection
djf6.	y02Bu	Fortral 50mg capsule
djfa.	y02By	Fortral 50mg suppository
djf9.	y02Bx	Fortral 60mg/2mL injection
djf3.	y02Br	Pentazocine 30mg/1mL injection
djf5.	y02Bt	Pentazocine 50mg suppository
x00RT	y03SX	Pentazocine 60mg/1mL injection
djf2.	y02Bq	Pentazocine hydrochloride 25mg tablet
djf1.	y02Bp	Pentazocine hydrochloride 50mg capsule
Dipipanone		
dj91.	y02Bb	Diconal tablet
dj92.	y02Bc	Dipipanone+cyclizine 10mg/30mg tablet
Buprenorphine		
dj3x.	y02Av	Buprenorphine 200micrograms sublingual tablet
dj3u.	y0ChF	Buprenorphine 2mg sublingual tablet
dj3y.	y02Aw	Buprenorphine 300micrograms/1mL injection
dj3t.	y0EcR	Buprenorphine 35micrograms/hour transdermal patch
dj35.	y02Au	Buprenorphine 400micrograms sublingual tablet
dj3s.	y0EcT	Buprenorphine 52.5micrograms/hour transdermal patch
dj3z.	y00Iy	Buprenorphine 600micrograms/2mL injection
dj3r.	y0EcV	Buprenorphine 70micrograms/hour transdermal patch
dj3v.	y0ChG	Buprenorphine 8mg sublingual tablet
dj3J.	yz7Rn	HAPOCTASIN 35micrograms/hour patches
dj3I.	yz7Rm	HAPOCTASIN 52.5micrograms/hour patches
dj3H.	yz7Rl	HAPOCTASIN 70micrograms/hour patches
dj3L.	yz7sZ	NATZON 2mg sublingual tablets
dj3K.	yz7sY	NATZON 400micrograms sublingual tablets
dj3M.	yz7sa	NATZON 8mg sublingual tablets
dj3d.	yz5pv	PREFIBIN 2mg sublingual tablets
dj3c.	yz5pu	PREFIBIN 400micrograms sublingual tablets
dj3e.	yz5pw	PREFIBIN 8mg sublingual tablets
dj37.	y0ChH	Subutex 2mg sublingual tablet
dj36.	y0ChE	Subutex 400micrograms sublingual tablet
dj38.	y0ChI	Subutex 8mg sublingual tablet
dj31.	y02Ar	Temgesic 200mcg sublingual tablet
dj32.	y02As	Temgesic 300micrograms/1mL injection
dj34.	y02At	Temgesic 400mcg sublingual tablet
dj33.	y00Ix	Temgesic 600micrograms/2mL injection
dj3f.	yz5px	TEPHINE 200micrograms sublingual tablets
dj3g.	yz5py	TEPHINE 400micrograms sublingual tablets
dj39.	y0EcS	Transtec 35micrograms/hour transdermal patch
dj3a.	y0EcU	Transtec 52.5micrograms/hour transdermal patch

dj3b.	y0EcW	Transtec 70micrograms/hour transdermal patch
Diamorphine		
dj7A.	y02BO	Diagesil 100mg injection (pdr for recon)
dj78.	y02BM	Diagesil 10mg injection (pdr for recon)
dj79.	y02BN	Diagesil 30mg injection (pdr for recon)
dj7B.	y02BP	Diagesil 500mg injection (pdr for recon)
dj77.	y02BL	Diagesil 5mg injection (pdr for recon)
cg31.	y00DR	Diamorphine 3mg/5mL linctus
dj75.	y02BJ	Diamorphine hydrochloride 100mg injection
dj73.	y02BH	Diamorphine hydrochloride 10mg injection
dj71.	y02BF	Diamorphine hydrochloride 10mg tablet
dj74.	y02BI	Diamorphine hydrochloride 30mg injection
dj76.	y02BK	Diamorphine hydrochloride 500mg injection
dj72.	y02BG	Diamorphine hydrochloride 5mg injection
dj22.	y00Is	Diamorphine simple elixir
dj7F.	y07bN	Diaphine 100mg injection (pdr for recon)
dj7D.	y07bL	Diaphine 10mg injection (pdr for recon)
dj7E.	y07bM	Diaphine 30mg injection (pdr for recon)
dj7G.	y07bO	Diaphine 500mg injection (pdr for recon)
dj7C.	y07bK	Diaphine 5mg injection (pdr for recon)
Hydromorphone		
djj1.	y0ADO	Hydromorphone hydrochloride 1.3mg capsule
djj8.	y0ADW	Hydromorphone hydrochloride 16mg m/r capsule
djj3.	y0ADQ	Hydromorphone hydrochloride 2.6mg capsule
djj9.	y0ADX	Hydromorphone hydrochloride 24mg m/r capsule
djj5.	y0ADT	Hydromorphone hydrochloride 2mg m/r capsule
djj6.	y0ADU	Hydromorphone hydrochloride 4mg m/r capsule
djj7.	y0ADV	Hydromorphone hydrochloride 8mg m/r capsule
djj2.	y0ADP	Palladone 1.3mg capsule
djj4.	y0ADR	Palladone 2.6mg capsule
djjD.	y0ADb	Palladone-SR 16mg m/r capsule
djjE.	y0ADc	Palladone-SR 24mg m/r capsule
djjA.	y0ADY	Palladone-SR 2mg m/r capsule
djjB.	y0ADZ	Palladone-SR 4mg m/r capsule
djjC.	y0ADa	Palladone-SR 8mg m/r capsule
Morphine		
x025k	y02AH	Cyclimorph 10 injection
x025l	y02AJ	Cyclimorph 15 injection
dj1c.	y07BJ	Cyclimorph-10 injection 1mL
dj1d.	y07BK	Cyclimorph-15 injection 1mL
dj1e.	y00Ii	Duromorph 64mg/1mL m/r injection
djy9.	y0ElT	Filnarine SR 100mg m/r tablet
djy6.	y0ElQ	Filnarine SR 10mg m/r tablet
djy7.	y0ElR	Filnarine SR 30mg m/r tablet
djy8.	y0ElS	Filnarine SR 60mg m/r tablet
dj1q.	y02AY	Min-I-Jet Morphine sulphate 20mg/2mL prefilled syringe
djzY.	y09wG	Morcap SR 100mg m/r capsule
djzb.	y09wK	Morcap SR 20mg m/r capsule
djzc.	y09wL	Morcap SR 50mg m/r capsule
djyD.	y0FOi	Morphgesic SR 100mg m/r tablet
djyA.	y0FOf	Morphgesic SR 10mg m/r tablet
djyB.	y0FOg	Morphgesic SR 30mg m/r tablet
djyC.	y0FOh	Morphgesic SR 60mg m/r tablet
dj2..	y00Iq	Morphine analgesic elixirs
x00Xt	y03SL	Morphine hydrochloride 10mg/mL oral solution
dj1S.	y02Ad	Morphine hydrochloride 15mg suppository
dj1T.	y02Af	Morphine hydrochloride 30mg suppository
dj21.	y00Ir	Morphine simple elixir
dj11.	y08D1	Morphine sulph [CNS] 10mg injection
dj12.	y08D2	Morphine sulph [CNS] 15mg injection
dj13.	y08D3	Morphine sulphate [CNS] 20mg/1ml injection
dj15.	y08D5	Morphine sulphate [CNS] 20mg/2ml injection
dj14.	y08D4	Morphine sulphate [CNS] 30mg/1ml injection
dj16.	y08D6	Morphine sulphate [CNS] 30mg/2ml injection
dj17.	y08EF	Morphine sulphate [CNS] 40mg/2ml injection
dj18.	y08D7	Morphine sulphate [CNS] 60mg/2ml injection
djzG.	y08Pl	Morphine sulphate 100mg m/r capsule
djz8.	y02CF	Morphine sulphate 100mg m/r tablet

djzi.	y0APM	Morphine sulphate 100mg/50mL injection
djze.	y0A5o	Morphine sulphate 100mg/50mL prefilled syringe
dj1M.	y02AV	Morphine sulphate 100mg/5mL oral solution
dj1K.	y01CE	Morphine sulphate 100mg/5mL oral unit dose vial
djzB.	y01Ia	Morphine sulphate 100mg/sachet granules for suspension
o451.	y018v	Morphine sulphate 10mg injection
djzD.	y08Pi	Morphine sulphate 10mg m/r capsule
djz4.	y02CB	Morphine sulphate 10mg m/r tablet
dj1D.	y02AK	Morphine sulphate 10mg suppository
djz1.	y02C8	Morphine sulphate 10mg tablet
x02LZ	y02A7	Morphine sulphate 10mg/1mL injection
dj1O.	y0EbR	Morphine sulphate 10mg/1mL prefilled syringe
dj1L.	y02AU	Morphine sulphate 10mg/5mL oral solution
dj1G.	y01CD	Morphine sulphate 10mg/5mL oral unit dose vial
djzP.	y09lI	Morphine sulphate 120mg m/r capsule
djzQ.	y09lJ	Morphine sulphate 150mg m/r capsule
o452.	y018w	Morphine sulphate 15mg injection
djz5.	y02CC	Morphine sulphate 15mg m/r tablet
dj19.	y02AD	Morphine sulphate 15mg suppository
x02La	y02A8	Morphine sulphate 15mg/1mL injection
djyI.	y0Fk1	Morphine sulphate 1mg/mL Minijet 10mL prefilled syringe
djzR.	y09lK	Morphine sulphate 200mg m/r capsule
djz9.	y02CG	Morphine sulphate 200mg m/r tablet
djzC.	y01Ib	Morphine sulphate 200mg/sachet granules for suspension
djzZ.	y09wI	Morphine sulphate 20mg m/r capsule
dj1E.	y02AL	Morphine sulphate 20mg suppository
djz2.	y02C9	Morphine sulphate 20mg tablet
o453.	y02A9	Morphine sulphate 20mg/1mL injection
o455.	y018x	Morphine sulphate 20mg/2mL injection
x02Ld	y02AB	Morphine sulphate 20mg/2mL prefilled syringe
djzs.	y0CZh	Morphine sulphate 20mg/mL oral solution
dj1Q.	y02AZ	Morphine sulphate 20mg/sachet granules for suspension
djzE.	y08Pj	Morphine sulphate 30mg m/r capsule
djz6.	y02CD	Morphine sulphate 30mg m/r tablet
dj1a.	y02AE	Morphine sulphate 30mg suppository
o454.	y02AA	Morphine sulphate 30mg/1mL injection
o456.	y00lf	Morphine sulphate 30mg/2mL injection
djy5.	y0ERh	Morphine sulphate 30mg/30mL injection
dj1I.	y02AS	Morphine sulphate 30mg/5mL oral unit dose vial
dj1R.	y02Ab	Morphine sulphate 30mg/sachet granules for suspension
o457.	y00lg	Morphine sulphate 40mg/2mL injection
djza.	y09wJ	Morphine sulphate 50mg m/r capsule
djzL.	y09br	Morphine sulphate 50mg tablet
djzh.	y0APL	Morphine sulphate 50mg/50mL injection
djzd.	y0A5m	Morphine sulphate 50mg/50mL prefilled syringe
djz3.	y02CA	Morphine sulphate 5mg m/r tablet
djzF.	y08Pk	Morphine sulphate 60mg m/r capsule
djz7.	y02CE	Morphine sulphate 60mg m/r tablet
dj18.	y02AC	Morphine sulphate 60mg/2mL injection
djzA.	y01IZ	Morphine sulphate 60mg/sachet granules for suspension
djzO.	y09lH	Morphine sulphate 90mg m/r capsule
x0081	y03TP	Morphine tartrate+cyclizine
dj1i.	y02AR	MST Continus 100mg m/r tablet
dj1X.	y02An	MST Continus 100mg/sachet granules for suspension
dj1f.	y02AM	MST Continus 10mg m/r tablet
dj1z.	y02Ap	MST Continus 15mg m/r tablet
dj1t.	y02Ae	MST Continus 200mg m/r tablet
dj1Y.	y01IY	MST Continus 200mg/sachet granules for suspension
dj1N.	y02AW	MST Continus 20mg/sachet granules for suspension
dj1g.	y02AO	MST Continus 30mg m/r tablet
dj1P.	y02AX	MST Continus 30mg/sachet granules for suspension
dj1y.	y02Ao	MST Continus 5mg m/r tablet
dj1h.	y02AP	MST Continus 60mg m/r tablet
dj1W.	y02Al	MST Continus 60mg/sachet granules for suspension
djzV.	y09lO	MXL 120mg m/r capsule
djzW.	y09lP	MXL 150mg m/r capsule
djzX.	y09lQ	MXL 200mg m/r capsule
djzS.	y09lL	MXL 30mg m/r capsule

djzT.	y09lM	MXL 60mg m/r capsule
djzU.	y09lN	MXL 90mg m/r capsule
dj1k.	y00Ik	Nepenthe 4.2mg/0.5mL injection
dj1j.	y00Ij	Nepenthe 8.4mg/mL elixir
dj1b.	y00Ih	Opium 10mg/mL tincture
dj1J.	y02AT	Oramorph 100mg/5mL oral unit dose vial
dj1l.	y00Il	Oramorph 10mg/5mL liquid 100mL
dj1p.	y00Ip	Oramorph 10mg/5mL liquid 250mL
dj1m.	y00Im	Oramorph 10mg/5mL liquid 500mL
dj1Z.	y0CP9	Oramorph 10mg/5mL oral solution 300mL
dj1F.	y02AN	Oramorph 10mg/5mL oral unit dose vial
dj1H.	y02AQ	Oramorph 30mg/5mL oral unit dose vial
dj1o.	y00Io	Oramorph concentrated 20mg/mL liquid 120mL
dj1n.	y00In	Oramorph concentrated 20mg/mL liquid 30mL
dj1x.	y02Am	Oramorph SR 100mg m/r tablet
dj1u.	y02Ag	Oramorph SR 10mg m/r tablet
dj1v.	y02Ai	Oramorph SR 30mg m/r tablet
dj1w.	y02Ak	Oramorph SR 60mg m/r tablet
djzp.	y0C8f	Pharma-Ject Morphine sulphate 100mg/50mL prefilled syringe
djzo.	y0C8e	Pharma-Ject Morphine sulphate 50mg/50mL prefilled syringe
djzg.	y0A5q	Rapiject Morphine sulphate 100mg/50mL prefilled syringe
djzf.	y0A5p	Rapiject Morphine sulphate 50mg/50mL prefilled syringe
djyH.	y0FOp	Rhotard SR 100mg m/r tablet
djyE.	y0FOm	Rhotard SR 10mg m/r tablet
djyF.	y0FOn	Rhotard SR 30mg m/r tablet
djyG.	y0FOo	Rhotard SR 60mg m/r tablet
dj1A.	y02AF	Sevredol 10mg suppository
dj1r.	y02Aa	Sevredol 10mg tablet
djzq.	y0Cai	Sevredol 10mg/5mL oral solution 100mL
djzt.	y0Caj	Sevredol 10mg/5mL oral solution 300mL
djzu.	y0Cak	Sevredol 10mg/5mL oral solution 500mL
dj1B.	y02AG	Sevredol 20mg suppository
dj1s.	y02Ac	Sevredol 20mg tablet
djzv.	y0Cam	Sevredol 20mg/mL concentrated oral solution 120mL
djzr.	y0Cal	Sevredol 20mg/mL concentrated oral solution 30mL
dj1C.	y02AI	Sevredol 30mg suppository
djzM.	y09bs	Sevredol 50mg tablet
djzm.	y0AVM	Zomorph 100mg m/r capsule
djzj.	y0AVJ	Zomorph 10mg m/r capsule
djzn.	y0AVN	Zomorph 200mg m/r capsule
djzk.	y0AVK	Zomorph 30mg m/r capsule
djzl.	y0AVL	Zomorph 60mg m/r capsule
Papavertum		
o474.	y018y	Omnopon 10mg tablet
o479.	y01HL	Omnopon 15.4mg/1mL injection
o4b2.	y04F1	Omnopon Paediatric 7.84mg/1mL injection
o47y.	y0192	Papaveretum 10mg tablet
o478.	y01HK	Papaveretum BP 15.4mg/1mL injection
o47A.	y080f	Papaveretum BP 7.7mg/1mL injection
Oxycodone		
djm4.	yz7wY	DOLOCODON PR 10mg m/r tablets
djm5.	yz7wZ	DOLOCODON PR 20mg m/r tablets
djm6.	yz7wa	DOLOCODON PR 40mg m/r tablets
djm3.	yz7wX	DOLOCODON PR 5mg m/r tablets
djkM.	yz60c	LONGTEC 10mg m/r tablets
djkN.	yz60d	LONGTEC 20mg m/r tablets
djkO.	yz60e	LONGTEC 40mg m/r tablets
djkL.	yz60b	LONGTEC 5mg m/r tablets
djkP.	yz60f	LONGTEC 80mg m/r tablets
djkW.	yz7GB	LYNLOR 10mg capsules
djkX.	yz7GC	LYNLOR 20mg capsules
djkV.	yz7GA	LYNLOR 5mg capsules
djki.	yz3Lx	OXYCODONE HCL+NALOXONE HCL 40mg/20mg m/r tablets
djkj.	yz3Ly	OXYCODONE HCL+NALOXONE HCL 5mg/2.5mg m/r tablets
djku.	y0D6X	Oxycodone hydrochloride 10mg capsule
djkw.	y0D6M	Oxycodone hydrochloride 10mg m/r tablet
djks.	y0D6d	Oxycodone hydrochloride 10mg/mL concentrate s/f liquid

djko.	y0FPs	Oxycodone hydrochloride 10mg/mL injection solution 1mL ampoule
djkn.	y0FQ1	Oxycodone hydrochloride 10mg/mL injection solution 2mL ampoule
djke.	yz4vQ	OXYCODONE HYDROCHLORIDE 120mg m/r tablets
djkh.	yz4vT	OXYCODONE HYDROCHLORIDE 15mg m/r tablets
djkv.	y0D6Y	Oxycodone hydrochloride 20mg capsule
djkx.	y0D6N	Oxycodone hydrochloride 20mg m/r tablet
djkg.	yz4vS	OXYCODONE HYDROCHLORIDE 30mg m/r tablets
djky.	y0D6O	Oxycodone hydrochloride 40mg m/r tablet
djkk.	yz3I5	OXYCODONE HYDROCHLORIDE 50mg/1mL soln for injection ampoules
djkt.	y0D6W	Oxycodone hydrochloride 5mg capsule
djkq.	y0EiX	Oxycodone hydrochloride 5mg m/r tablet
djkr.	y0D6c	Oxycodone hydrochloride 5mg/5mL s/f liquid
djkf.	yz4vR	OXYCODONE HYDROCHLORIDE 60mg m/r tablets
djkz.	y0D6P	Oxycodone hydrochloride 80mg m/r tablet
djkm.	y0JFp	OXYCODONE HYDROCHLORIDE+NALOXONE HYDROCHLORIDE 10mg/5mg m/r tablets
djkl.	y0JFo	OXYCODONE HYDROCHLORIDE+NALOXONE HYDROCHLORIDE 20mg/10mg m/r tablets
djk4.	y0D6Q	OxyContin 10mg m/r tablet
djkK.	yz4vP	OXYCONTIN 120mg m/r tablets
djkH.	yz4vM	OXYCONTIN 15mg m/r tablets
djk5.	y0D6R	OxyContin 20mg m/r tablet
djkI.	yz4vN	OXYCONTIN 30mg m/r tablets
djk6.	y0D6S	OxyContin 40mg m/r tablet
djkp.	y0EiY	OxyContin 5mg m/r tablet
djkJ.	yz4vO	OXYCONTIN 60mg m/r tablets
djk7.	y0D6T	OxyContin 80mg m/r tablet
djkR.	yz61P	OXYLAN 10mg m/r tablets
djkS.	yz61Q	OXYLAN 20mg m/r tablets
djkT.	yz61R	OXYLAN 40mg m/r tablets
djkQ.	yz61O	OXYLAN 5mg m/r tablets
djkU.	yz61S	OXYLAN 80mg m/r tablets
djk2.	y0D6a	OxyNorm 10mg capsule
djk9.	y0D6f	OxyNorm 10mg/mL concentrate liquid
djkA.	y0FPw	OxyNorm 10mg/mL injection solution 1mL ampoule
djkB.	y0FQ4	OxyNorm 10mg/mL injection solution 2mL ampoule
djk3.	y0D6b	OxyNorm 20mg capsule
djkE.	yz3I4	OXYNORM 50mg/1mL solution for injection ampoules
djk1.	y0D6Z	OxyNorm 5mg capsule
djk8.	y0D6e	OxyNorm 5mg/5mL liquid
djkc.	yz7sc	RELTEBON 10mg m/r tablets
djkd.	yz7sd	RELTEBON 20mg m/r tablets
djm1.	yz7sf	RELTEBON 40mg m/r tablets
djkb.	yz7sb	RELTEBON 5mg m/r tablets
djm2.	yz7sg	RELTEBON 80mg m/r tablets
djkZ.	yz7Zl	SHORTEC 10mg capsules
djka.	yz7Zm	SHORTEC 20mg capsules
djkY.	yz7Zk	SHORTEC 5mg capsules
djkC.	y0JFm	TARGINACT 10mg/5mg m/r tablets
djkD.	y0JFn	TARGINACT 20mg/10mg m/r tablets
djkG.	yz3Lw	TARGINACT 40mg/20mg m/r tablets
djkF.	yz3Lv	TARGINACT 5mg/2.5mg m/r tablets
Pethidine		
djg1.	y00JF	Pethidine 25mg paediatric tablet
djg2.	y02C0	Pethidine hydrochloride 50mg tablet
o483.	y02C1	Pethidine hydrochloride 50mg/1mL injection
djg6.	y00JG	Pethilorfan 50mg/1mL injection
djg3.	y08DA	Pethidine [analg] 50mg/1ml injection
o484.	y07a4	Pethidine hydrochloride 100mg/2mL injection
o481.	y03SV	Pethidine hydrochloride 50mg/5mL injection
o482.	y03SW	Pethidine hydrochloride 100mg/10mL injection
djg8.	y02C4	Pethidine hydrochloride+promethazine hydrochloride 100mg/50mg/2mL injection
djg5.	y02C3	Pamergan P100 injection
djg7.	y00JH	Pethilorfan 100mg/2mL injection

Methadone		
djcy.	y02Bh	Methadone hydrochloride 5mg tablet
djc1.	y02Be	Physeptone 5mg tablet
Tapentadol		
	yz4vL	TAPENTADOL 50mg m/r tablets
	yz4vH	TAPENTADOL 250mg m/r tablets
	yz4vI	TAPENTADOL 200mg m/r tablets
	yz4vK	TAPENTADOL 100mg m/r tablets
	yz4vG	TAPENTADOL 50mg tablets
	yz7Tu	TAPENTADOL 20mg/mL oral solution
	yz4vJ	TAPENTADOL 150mg m/r tablets
	yz4vF	TAPENTADOL 75mg tablets
	yz4v9	PALEXIA SR 100mg m/r tablets
	yz4vB	PALEXIA SR 200mg m/r tablets
	yz4vC	PALEXIA SR 250mg m/r tablets
	yz4vA	PALEXIA SR 150mg m/r tablets
	yz4v8	PALEXIA SR 50mg m/r tablets
	yz4vD	PALEXIA 50mg tablets
	yz4vE	PALEXIA 75mg tablets
	yz7Tt	PALEXIA 20mg/mL oral solution

A.5 Population estimates

Table A.3: Calculating population estimates per Health Board

% of total Welsh population	Wales Total	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB
	100%	17%	19%	22%	16%	10%	12%	4%
2005	2969300	504,781	564,167	653246	475088	296930	356316	118772
2006	2985700	507,569	567,283	656854	477712	298570	358284	119428
2007	3006300	511,071	571,197	661386	481008	300630	360756	120252
2008	3025900	514,403	574,921	665698	484144	302590	363108	121036
2009	3038872	512,921	572,518	684,575	463,818	292,899	379,051	133,090
2010	3049971	515,420	574,778	685,911	467,837	292,952	380,195	132,878
2011	3063758	517,981	577,077	688,417	472,121	293,224	381,867	133,071
2012	3074067	519,481	577,981	690,434	475,324	294,497	383,398	132,952
2013	3082412	520,710	579,101	691,986	478,869	295,135	383,906	132,705
2014	3092036	523,001	580,401	694,038	481,979	295,953	383,989	132,675
2015	3099086	525,466	581,789	694,473	484,752	296,735	383,229	132,642

ABMUHB = Abertawe Bro Morgannwg University Health Board, ABUHB = Aneurin Bevan University Health Board, BCUHB = Betsi Cadwaladr University Health Board, CVUHB = Cardiff and Vale University Health Board, CTUHB = Cwm Taf University Health Board, HDUHB = Hywel Dda University Health Board, PTHB = Powys Teaching Health Board

Table A.4: Percentage of each Health Board primary care population represented within SAIL databank

Health Board	Percentage represented in SAIL databank
Abertawe Bro Morgannwg University Health Board	96%
Aneurin Bevan University Health Board	70%
Betsi Cadwaladr University Health Board	75%
Cardiff and Vale University Health Board	80%
Cwm Taf University Health Board	77%
Hywel Dda University Health Board	81%
Powys Teaching Health Board	41%

Table A.5: Calculated annual SAIL databank population per Health Board

SAIL	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB
2005	484590	394917	489935	380070	228636	288616	48697
2006	487266	397098	492641	382170	229899	290210	48965
2007	490628	399838	496040	384806	231485	292212	49303

2008	493827	402445	499274	387315	232994	294117	49625
2009	492404	400763	513431	371054	225532	307031	54567
2010	494803	402345	514433	374270	225573	307958	54480
2011	497262	403954	516313	377697	225782	309312	54559
2012	498702	404587	517826	380259	226763	310552	54510
2013	499882	405371	518990	383095	227254	310964	54409
2014	502081	406281	520529	385583	227884	311031	54397
2015	504447	407252	520855	387802	228486	310415	54383

Table A.6: Health Board populations per 1000 population

SAIL/1000	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB
2005	484.6	394.9	489.9	380.1	228.6	288.6	48.7
2006	487.3	397.1	492.6	382.2	229.9	290.2	49.0
2007	490.6	399.8	496.0	384.8	231.5	292.2	49.3
2008	493.8	402.4	499.3	387.3	233.0	294.1	49.6
2009	492.4	400.8	513.4	371.1	225.5	307.0	54.6
2010	494.8	402.3	514.4	374.3	225.6	308.0	54.5
2011	497.3	404.0	516.3	377.7	225.8	309.3	54.6
2012	498.7	404.6	517.8	380.3	226.8	310.6	54.5
2013	499.9	405.4	519.0	383.1	227.3	311.0	54.4
2014	502.1	406.3	520.5	385.6	227.9	311.0	54.4
2015	504.4	407.3	520.9	387.8	228.5	310.4	54.4

Table A.7: SAIL population – based on 78% of Welsh primary care population represented within the Databank

Year	All Wales	SAIL	Population/1000
2005	2969309	2315460	2315.46014
2006	2985668	2328249	2328.24886
2007	3006299	2344313	2344.31274
2008	3025867	2359597	2359.59682
2009	3038872	2364783	2364.78285
2010	3049971	2373862	2373.86162
2011	3063758	2384879	2384.87907
2012	3074067	2393199	2393.19855
2013	3082412	2399964	2399.96386
2014	3092036	2407785	2407.78501
2015	3099086	2413641	2413.64067

Table A.8: SAIL population by gender

	Male	Female	Male%	Female%	MaleSAIL	Female SAIL	MaleSAIL /1000	FemaleSAIL/1000
2005	1447755	1521554	48.8%	51.2%	1128956	1186504	1129.0	1186.5
2006	1455660	1530008	48.8%	51.2%	1135136	1193113	1135.1	1193.1
2007	1468535	1537764	48.8%	51.2%	1145164	1199149	1145.2	1199.1
2008	1479395	1546472	48.9%	51.1%	1153645	1205952	1153.6	1206.0
2009	1487848	1551024	49.0%	51.0%	1157810	1206973	1157.8	1207.0
2010	1495493	1554478	49.0%	51.0%	1163976	1209885	1164.0	1209.9
2011	1504475	1559283	49.1%	50.9%	1171108	1213771	1171.1	1213.8
2012	1509936	1564131	49.1%	50.9%	1175504	1217695	1175.5	1217.7
2013	1515227	1567185	49.2%	50.8%	1179755	1220209	1179.8	1220.2
2014	1521315	1570721	49.2%	50.8%	1184656	1223129	1184.7	1223.1
2015	1525561	1573525	49.2%	50.8%	1188143	1225498	1188.1	1225.5

Table A.9: Percentage gender split by Health Board

	Female	**Male**
ABMUHB	50.5%	49.5%
ABUHB	51.0%	49.0%

BCUHB	50.7%	49.3%
CTUHB	51.0%	49.0%
CVUHB	50.9%	49.1%
HDUHB	50.8%	49.2%
PTHB	50.5%	49.5%

Table A.10: Health Board populations (aged 18 years and over) by gender and age-group

2015 data							
Women	**18-24**	**25-44**	**45-64**	**65 to 74**	**75 to 84**	**85 +**	**Total**
BCUHB	27,170	77,742	95,580	43,692	26,454	12,978	351,485
PTHB	4,220	12,914	19,726	9,473	5,669	2,905	67,025
HDUHB	16,795	39,885	54,080	25,230	15,147	7,432	194,519
ABMUHB	23,379	64,372	70,355	29,650	18,752	8,528	265,264
CTUHB	13,361	38,153	39,168	16,154	9,597	4,209	151,187
ABUHB	23,853	72,094	79,627	32,656	19,742	8,775	296,777
CVUHB	32,704	64,627	58,379	21,095	14,135	7,112	247,268
Men	**18-24**	**25-44**	**45-64**	**65 to 74**	**75 to 84**	**85 +**	**Total**
BCUHB	29,627	78,107	91,253	42,142	22,250	6,908	341,875
PTHB	4,839	12,888	19,048	9,363	5,104	1,643	65,705
HDUHB	19,089	38,662	51,019	24,442	13,283	4,115	188,610
ABMUHB	27,386	65,814	67,107	26,980	14,722	4,485	260,257
CTUHB	14,143	36,545	37,914	15,245	7,805	2,117	145,438
ABUHB	25,040	68,748	77,346	30,638	16,308	4,600	285,468
CVUHB	31,389	67,026	55,251	19,337	10,407	3,494	238,208

Table A.11: SAIL databank population per 1000 by age-group

	Population/1000 per age-group (years)					
Year	**18-24**	**25-44**	**45-64**	**65-74**	**75-84**	**85+**
2005	268.312	771.909	762.367	272.062	185.366	62.324
2006	273.651	771.538	773.165	273.704	184.364	65.875
2007	280.233	771.48	783.638	277.502	183.512	68.86
2008	284.388	770.558	792.625	283.815	183.985	70.601
2009	288.48	766.376	800.144	290.886	184.576	72.135
2010	292.336	759.521	807.755	297.052	186.469	73.734
2011	295.923	754.452	814.557	302.703	188.359	75.331
2012	300.246	745.539	811.498	318.14	190.806	76.932
2013	298.455	742.365	810.751	329.493	193.839	77.298
2014	295.506	738.476	813.698	338.448	197.433	78.866
2015	292.995	737.577	815.853	346.097	199.375	79.301

Table A.12: Annual populations by gender and by Health Board, based on percentage gender split

Female							
SAIL	**ABMUHB**	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**	**PTHB**
2005	244.6	201.3	248.4	193.7	116.5	146.5	24.6
2006	246.0	202.4	249.7	194.8	117.1	147.3	24.7
2007	247.7	205.1	251.5	196.1	117.9	148.4	24.9
2008	249.3	205.1	253.1	197.4	118.7	149.3	25.1
2009	248.5	204.3	260.3	189.1	114.9	155.9	27.6
2010	249.8	205.1	260.8	190.8	114.9	156.4	27.5
2011	251.0	205.9	261.7	192.5	115.0	157.0	27.6
2012	251.7	206.2	262.5	193.8	115.5	157.7	27.5
2013	252.3	206.6	263.1	195.3	115.7	157.9	27.5
2014	253.4	207.1	263.9	196.5	116.1	157.9	27.5
2015	254.6	207.6	264.0	197.7	116.4	157.6	27.5
Male							
SAIL	**ABMUHB**	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**	**PTHB**
2005	240.0	193.6	241.6	186.4	112.2	142.1	24.1
2006	241.3	194.7	242.9	187.4	112.8	142.9	24.2

2007	243.0	196.0	244.6	188.7	113.6	143.9	24.4
2008	244.6	197.3	246.2	189.9	114.3	144.8	24.6
2009	243.9	196.5	253.2	181.9	110.7	151.1	27.0
2010	245.0	197.3	253.7	183.5	110.7	151.6	27.0
2011	246.3	198.1	254.6	185.2	110.8	152.3	27.0
2012	247.0	198.4	255.3	186.4	111.3	152.9	27.0
2013	247.6	198.7	255.9	187.8	111.5	153.1	26.9
2014	248.6	199.2	256.7	189.1	111.8	153.1	26.9
2015	249.8	199.7	256.8	190.1	112.1	152.8	26.9

Appendix B General trends

B.1.1 Trends in number of people

The number of people receiving opioid prescriptions increased by 19.4% (from 126.2 to 150.6 per 1000 population) between 2005 and 2015 (Figure B.1). Spearman's Rho confirmed the positive trend (r=0.827, p<0.01). The trend in population adjusted number of people, was similar to the empirical trend in numbers (Table B.1).

Table B.1: Trends in the number of people receiving opioid prescriptions, 2005 - 2015 and stratified by opioid type

	Non-cancer n=1,099,026								
	Total			Weak opioids			Strong opioids		
Year	Number of people	People per 1000 population	Annual change * (%)	Number of people	People per 1000 population	Annual change* (%)	Number of people	People per 1000 population	Annual change* (%)
2005	292,209	126.2		281,978	121.8		10,231	4.4	
2006	298,838	128.4	1.7	287,449	123.5	1.4	11,389	4.9	10.7
2007	321,430	137.1	6.8	308,614	131.6	6.6	12,816	5.5	11.8
2008	336,377	142.6	4.0	322,315	136.6	3.8	14,062	6.0	9.0
2009	348,136	147.2	3.3	332,543	140.6	2.9	15,593	6.6	10.6
2010	356199	150.1	1.9	339,198	142.9	1.6	17,001	7.2	8.6
2011	363,861	152.6	1.7	345,031	144.7	1.2	18,830	7.9	10.2
2012	368,869	154.1	1.0	347,299	145.1	0.3	21,570	9.0	14.2
2013	366,047	152.5	-1.0	341,700	142.4	-1.9	24,347	10.1	12.6
2014	366,903	152.4	-0.1	338,652	140.6	-1.2	28,251	11.7	15.7
2015	363,560	150.6	-1.2	331,555	137.4	-2.3	32,005	13.3	13.0
Percentage change (%) 2005 - 2015	24.4	19.3		17.6	12.8		212.8	202.3	
Spearman's r, p-value**	0.882, p<.001**	0.827, p<0.01*		0.945, p<.001**	0.909, p<.001**		>.999, p<.001**	>.999, p<.001**	

*based on people per thousand population**p<0.05 = statistically significant

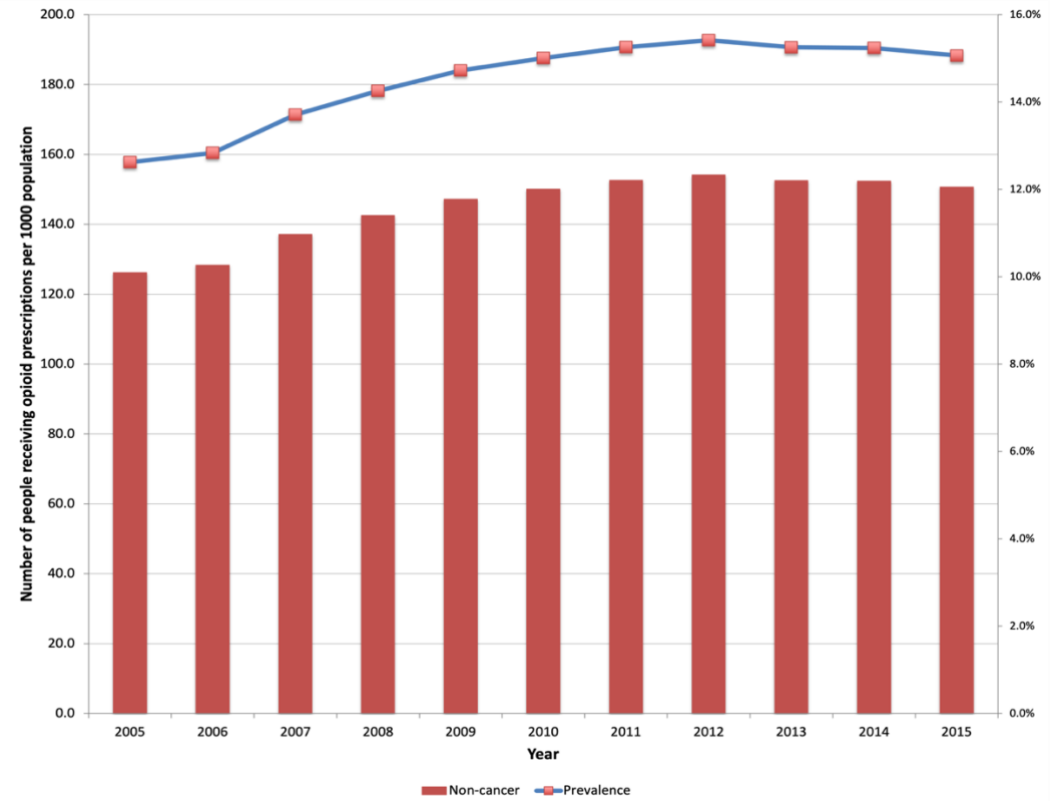


Figure B.1: Number of people receiving prescriptions for opioids between 2005 - 2015 and prescribing prevalence

B.1.2 Prevalence of people prescribed opioids in SAIL databank population

The prevalence of non-cancer related opioid prescribing in the SAIL databank population was calculated at 12.6% in 2005 and peaked in 2012 at 15.4% (Figure B.1). After that, a small annual reduction led to a non-cancer opioid prescribing prevalence of 15.1% in 2015 (Table B.2). Over the same period, the Welsh population increased by 4.4% (Figure B.2)

The largest annual increases in the number of people receiving opioid prescriptions were observed between 2005 and 2010 (Figure B.2). In the second half of the study period, the annual percentage increase in numbers slowed and then started to reduce between 2012 and 2015 (Table B.1).

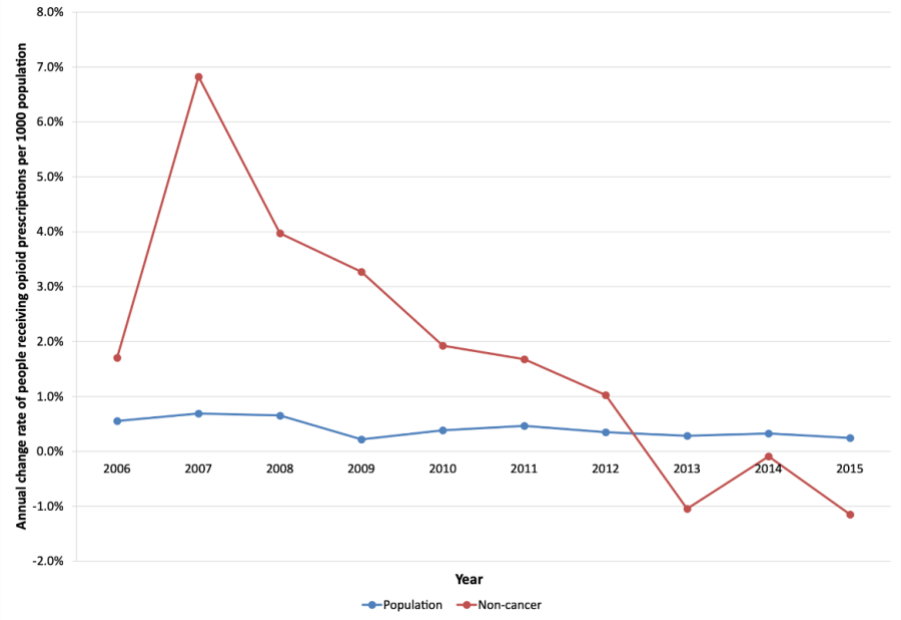


Figure B.2: Annual change rate of the number of people receiving opioid prescriptions and the Welsh population between 2006 – 2015

Table B.2: Determining prevalence of opioid prescribing in the SAIL databank population

Year	SAIL Databank population	Number of people prescribed opioid analgesics	Prevalence in SAIL Databank (%)	Annual percentage change in prevalence (%)
2005	2,315,460	292,209	12.6	1.7
2006	2,328,249	298,838	12.8	6.8
2007	2,344,313	321,430	13.7	4.0
2008	2,359,597	336,377	14.3	3.3
2009	2,364,783	348,136	14.7	1.9
2010	2,373,862	356,199	15.0	1.7
2011	2,384,879	363,861	15.3	1.0
2012	2,393,199	368,869	15.4	-1.0
2013	2,399,964	366,047	15.3	-0.1
2014	2,407,785	366,903	15.2	-1.2
2015	2,413,641	363,560	15.1	

B.2 Prescribing by drug-type

B.2.1 Trends in number of people by drug-type

From 2005 until 2015, the number of people per 1000 population receiving strong opioid prescriptions, tripled (Table B.1). In contrast to weak opioid prescribing, a faster increase in the rate was observed in the second half of the study period (Table B.3). Numbers of people receiving strong opioids rose 85.2% between 2010 and 2015 compared to 62.1% between 2005 and 2010 (Figure B.3).

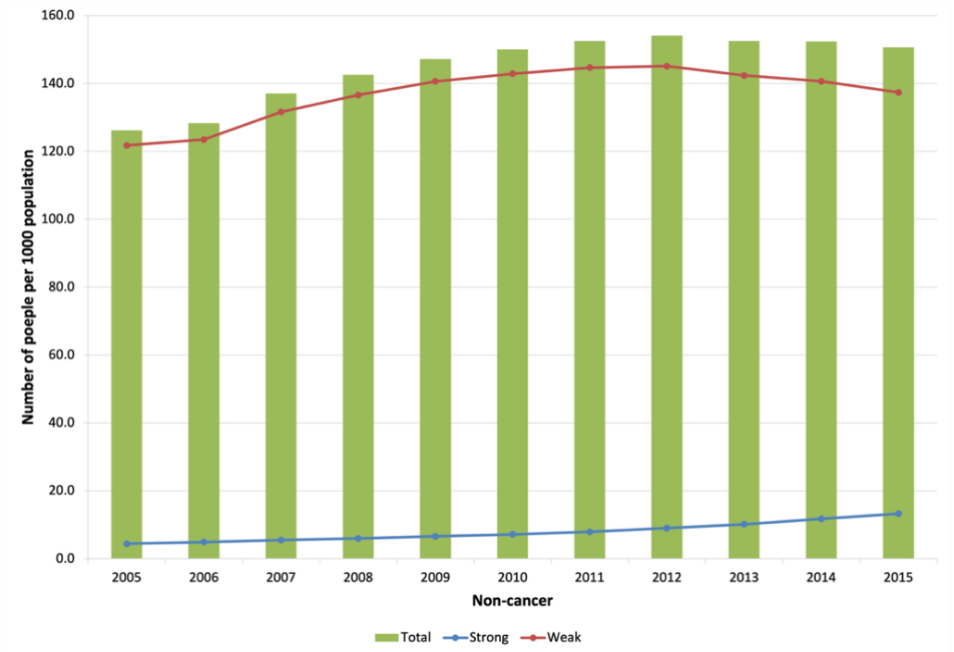


Figure B.3: Trends in the number of people receiving weak and strong opioid prescribing2005-2015

Between 2005 and 2015, strong opioid analgesic prescriptions were issued to 5.4% of all those who received prescriptions in that time. The percentage of people receiving strong opioids as a percentage of all people receiving opioid prescriptions each year, rose 151.4% (from 3.5% to 8.8% of all prescribing) in the 11-year period (Figure B.4).

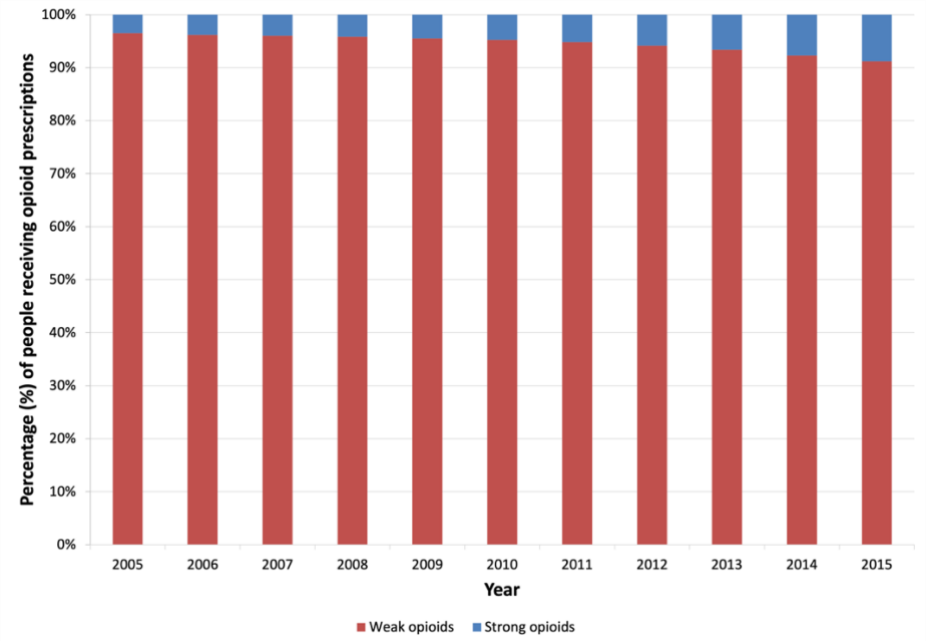


Figure B.4: Percentage of people receiving prescriptions for weak or strong opioids as a percentage of total number of people

Table B.3: Annual changes in opioid prescribing, stratified by opioid group

	Non-cancer n=22,786,565								
	Total			Weak opioids			Strong opioids		
Year	Number of prescriptions	Prescriptions per 1000 population	Annual change* (%)	Number of prescriptions	Prescriptions per 1000 population	Annual change* (%)	Number of prescriptions	Prescriptions per 1000 population	Annual change* (%)
2005	1,613,417	696.8		1,520,441	656.6		92,976	40.2	
2006	1,656,332	711.4	2.1	1,544,592	663.4	1.0	111,740	48.0	19.5
2007	1,783,100	760.6	6.9	1,651,974	704.7	6.2	131,126	55.9	16.5
2008	1,904,351	807.1	6.1	1,751,223	742.2	5.3	153,128	64.9	16.0
2009	2,002,551	846.8	4.9	1,828,130	773.1	4.2	174,421	73.8	13.7
2010	2,108,572	888.2	4.9	1,906,075	802.9	3.9	202,497	85.3	15.7
2011	2,227,037	933.8	5.1	1,990,199	834.5	3.9	236,838	99.3	16.4
2012	2,318,407	968.7	3.7	2,043,247	853.8	2.3	275,160	115.0	15.8
2013	2,358,706	982.8	1.5	2,044,810	852.0	-0.2	313,896	130.8	13.8
2014	2,398,718	996.2	1.4	2,048,026	850.6	-0.2	350,692	145.6	11.4
2015	2,415,374	1000.7	0.5	2,021,677	837.6	-1.5	393,697	163.1	12.0
Percentage change (%) 2005 - 2015	49.7	43.6		33.0	27.6		323.4	306.2	
Spearman's r, p-value**	>.999, p<.001**	>.999, p<.001**		0.945, p<.001**	0.909, p<.001**		>.999, p<.001**	>.999, p<.001**	

*based on prescriptions per thousand **p<0.05 = statistically significant

B.3 Trends in prescribing by gender

B.3.1 Trends in numbers of people by gender

Over the 11 years examined, significantly more women received weak opioid prescriptions compared to men (Mann-Whitney U test, U=121.00, SE=15.23, $p<.001$, $\eta^2=0.72$, $d_{Cohen}= 3.19$). Women composed 60.1% (2,147,966 women from 3,576,966 total) of the total number of people receiving prescriptions for weak opioids between 2005 and 2015 (Figure B.5). As previously observed, the difference in the number of men and women receiving prescriptions each year slightly reduced over the 11 years examined. The gap between annual numbers reduced by 11.1% (from 52.9% to 41.8% more women than men per 1000 population per year) by the end of the study period (Table B.4 and **Error! Reference source not found.**).

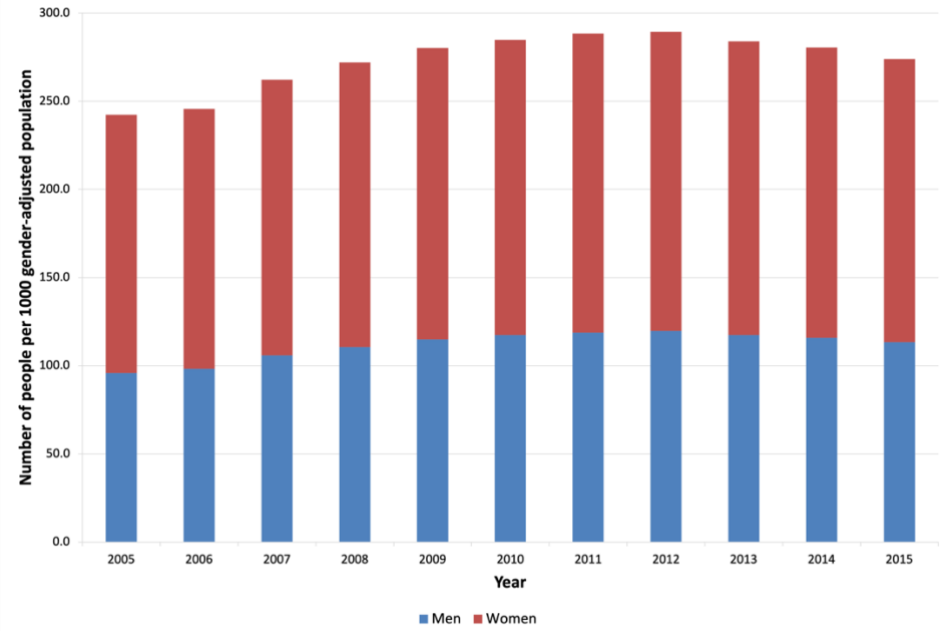


Figure B.5: Gender differences in the number of people receiving weak opioid prescriptions. Data presented adjusted for gender-population

Numbers of men and women receiving weak opioids peaked in 2012 (Figure B.5) as with the trend in all prescribing (Figure B.1). Women were observed to have an increase of 9.7% (from 146.5 to 160.7 women per 1000 gender-adjusted population) over the 11 years analysed (Spearman's $r=0.745$, $p<0.01$). An average 45% fewer men than women received weak opioid prescriptions each year (Table B.5). The increase in the number of men, however, was 18.3% (from 95.8 to 113.3 men per 1000 gender-adjusted population) (Table B.4) (Spearman's $r=0.764$, $p<0.01$).

Table B.4: Trends in the number of men receiving opioid prescriptions 2005 - 2015

Men									
	Total			Weak			Strong		
Year	Number of people	People per 1000 population	Annual change* (%)	Number of people	People per 1000 population	Annual change* (%)	Number of people	People per 1000 population	Annual change* (%)
2005	112,388	99.6		108,165	95.8		4,223	3.7	
2006	116,055	102.2	2.7	111,497	98.2	2.5	4,558	4.0	7.3
2007	126,294	110.3	7.9	121,287	105.9	7.8	5,007	4.4	8.9
2008	132,916	115.2	4.5	127,581	110.6	4.4	5,335	4.6	5.8
2009	138,875	119.9	4.1	133,033	114.9	3.9	5,842	5.0	9.1
2010	143,193	123.0	2.6	136,706	117.4	2.2	6,487	5.6	10.5
2011	146,295	124.9	1.5	139,165	118.8	1.2	7,130	6.1	9.2
2012	148,838	126.6	1.4	140,708	119.7	0.7	8,130	6.9	13.6
2013	147,604	125.1	-1.2	138,410	117.3	-2.0	9,194	7.8	12.7
2014	147,869	124.8	-0.2	137,188	115.8	-1.3	10,681	9.0	15.7
2015	146,629	123.4	-1.1	134,628	113.3	-2.2	12,001	10.1	12.0
Percentage change (%) 2005 - 2015	24.5	19.2		24.5	18.3		184.2	173.0	
Spearman's r, p-value**	0.918, p<.001**	0.845, p<0.01**		0.782, p<0.01**	0.664, p<0.05**		>.999, p<.001**	>.999, p<.001**	

*based on people per thousand **p<0.05 = statistically significant

Table B.5: Trends in the number of women receiving opioid prescriptions 2005 - 2015

Women									
	Total			Weak			Strong		
Year	Number of people	People per 1000 population	Annual change* (%)	Number of people	People per 1000 population	Annual change* (%)	Number of people	People per 1000 population	Annual change* (%)

	2005	179,821	151.6		173,813	146.5		6,008	5.1	
	2006	182,783	153.2	1.1	175,952	147.5	0.7	6,831	5.7	13.1
	2007	195,136	162.7	6.2	187,327	156.2	5.9	7,809	6.5	13.7
	2008	203,461	168.7	3.7	194,734	161.5	3.4	8,727	7.2	11.1
	2009	209,261	173.4	2.8	199,510	165.3	2.4	9,751	8.1	11.6
	2010	213,006	176.1	1.5	202,492	167.4	1.3	10,514	8.7	7.6
	2011	217,566	179.2	1.8	205,866	169.6	1.3	11,700	9.6	10.9
	2012	220,031	180.7	0.8	206,591	169.7	0.0	13,440	11.0	14.5
	2013	218,443	179.0	-0.9	203,290	166.6	-1.8	15,153	12.4	12.5
	2014	219,034	179.1	0.0	201,464	164.7	-1.1	17,570	14.4	15.7
	2015	216,931	177.0	-1.2	196,927	160.7	-2.4	20,004	16.3	13.6
Percentage change (%) 2005 - 2015		20.6	16.8		13.3	9.7		233.0	222.4	
Spearman's r, p-value**		0.882, p<.001**	0.836, p<0.01**		0.691, p<0.05**	0.555, p=0.077		>.999, p<.001**	>.999, p<.001**	

*based on people per thousand **p<0.05 = statistically significant

The annual number of men per 1000 population receiving opioid prescriptions increased 19.3% (from 99.6 to 123.4 people per 1000 gender-adjusted population) between 2005 and 2015 (Table B.4). A 16.8% (from 151.6 to 177.0 people per 1000 population) rise in the number of women receiving prescriptions was observed over the same period (Table B.5). Strong correlation between time and the change in number of people prescribed opioids, was significant for both genders based on Spearman's Rho results (Table B.4 and Table B.5). A Mann-Whitney U test confirmed the number of women receiving prescriptions was significantly greater than the number of men, over the 11 years analysed ($U=121.00$, $SD=15.23$, $p<.001$*, $\eta^2=0.72$, $d_{Cohen}= 3.19$).

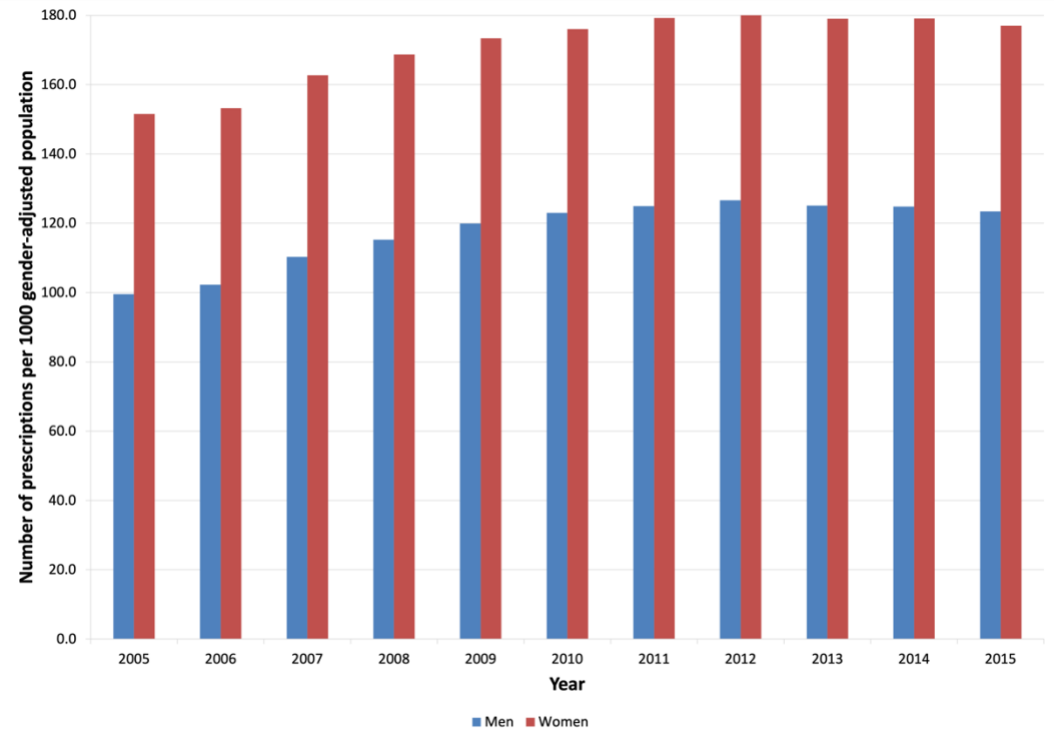


Figure B.6: Trends in the number of prescriptions for opioid analgesics displayed by annual, gender-adjusted population

Peak numbers of men and women were observed in 2012 and then began to slowly decline (Figure B.6). The difference between the number of men and women receiving opioid analgesic prescriptions each year grew proportionately less over time. In 2005, 52% more women than men received opioid prescriptions, but this reduced to 43% in 2015 (Table B.4 and Table B.5).

Large percentage increases in the number of men and women receiving strong opioid prescriptions were noted between 2005 and 2015 (Table B.4 and Table B.5). The number of women increased 222.4% (from 5.1 to 16.3 women per 1000 population) with very strong correlation observed by Spearman's Rho test (r=>.999, p<.001). Similarly, men had a very strongly correlated 170% (from 3.7 to 10.1 men per 1000 population) increase in numbers receiving strong opioids between 2005 and 2015 (Table B.4).

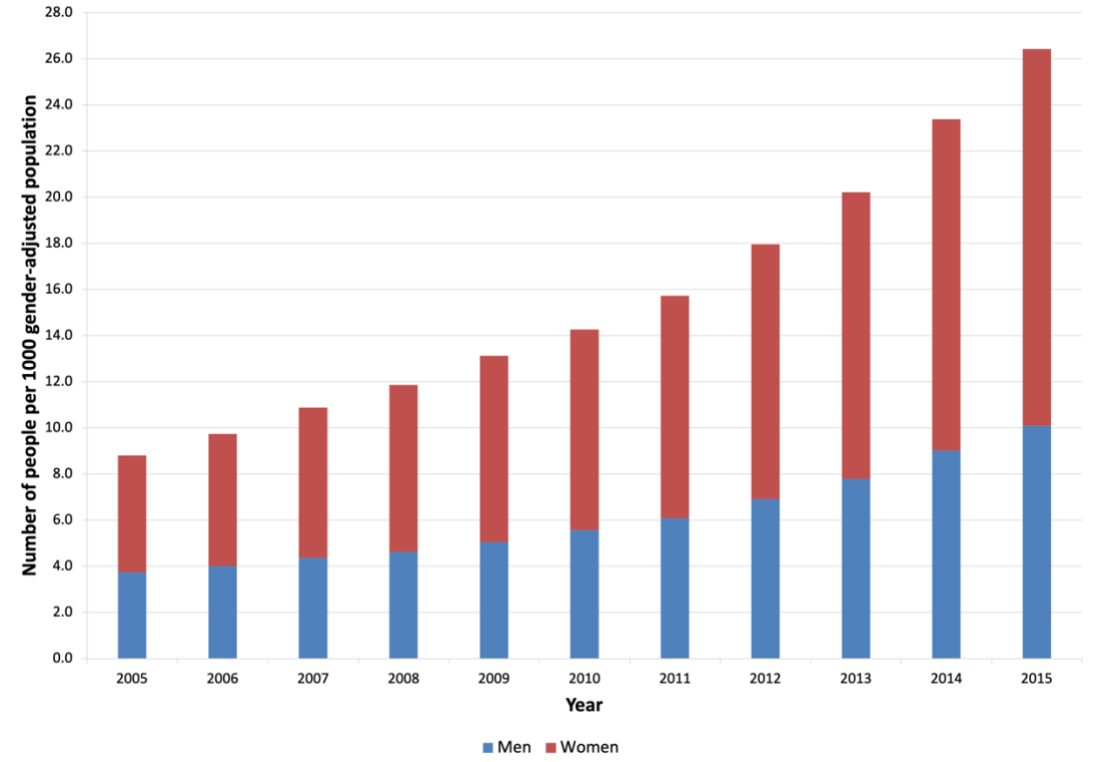


Figure B.7: Gender differences in the number of people receiving strong opioid prescriptions. Data presented adjusted for gender-population

Over the study period, significantly more women than men received strong opioid analgesics (Mann-Whitney U, U=98.00, SE=15.23, p<0.05, η^2=0.28, d_{Cohen}= 1.23). Women made up 62% (127,507 of 206,095 total number of people) of all people receiving strong opioid prescriptions between 2005 and 2015. Whilst both genders were observed to have large increases in number, the gap between men and women receiving prescriptions widened (Figure B.7). At the beginning of the study period in 2005, there were 35.4% (5.1 women per 1000 population versus 3.7 men per 1000 population) more women than men receiving strong opioid prescriptions. In 2015, the difference was 61.6% (16.3 women per 1000 population versus 10.1 men per 1000 population) (Table B.4 and Table B.5).

B.3.2 Trends in numbers of prescriptions by gender

Table B.6: Trends in the number of prescriptions issued to men and by opioid type

	Men								
	Total			Weak			Strong		
Year	Number of Rx	Rx per 1000 population	Annual change* (%)	Number of Rx	Rx per 1000 population	Annual change* (%)	Number of Rx	Rx per 1000 population	Annual change* (%)
2005	601,797	533.1		560,449	496.4		41,348	36.6	
2006	623,000	548.8	3.0	575,246	506.8	2.1	47,754	42.1	14.9
2007	675,953	590.3	7.5	620,623	542.0	6.9	55,330	48.3	14.9
2008	725,495	628.9	6.5	662,071	573.9	5.9	63,424	55.0	13.8
2009	769,076	664.3	5.6	699,022	603.7	5.2	70,054	60.5	10.1
2010	815,391	700.5	5.5	735,080	631.5	4.6	80,311	69.0	14.0
2011	866,271	739.7	5.6	772,484	659.6	4.4	93,787	80.1	16.1
2012	907,710	772.2	4.4	796,944	678.0	2.8	110,766	94.2	17.7
2013	924,056	783.3	1.4	799,842	678.0	0.0	124,214	105.3	11.7
2014	939,578	793.1	1.3	802,384	677.3	-0.1	137,194	115.8	10.0
2015	945,303	795.6	0.3	790,866	665.6	-1.7	154,437	130.0	12.2
Percentage change (%) 2005 - 2015	57.1	49.3		41.1	34.1		273.5	255.2	
Spearman's r, p -value**	>.999, p<.001**	>.999, p<.001**		0.945, p<0.005**	0.909, p<.001**		>.999, p<.001**	>.999, p<.001**	

Rx=prescriptions

Table B.7: Trends in the number of prescriptions issued to women and by opioid type

	Women								
	Total			Weak			Strong		
Year	Number of Rx	Rx per 1000 population	Annual change* (%)	Number of Rx	Rx per 1000 population	Annual change* (%)	Number of Rx	Rx per 1000 population	Annual change* (%)

	2005	1,011,620	852.6		959,992	809.1		51,628	43.5	
	2006	1,033,332	866.1	1.6	969,346	812.5	0.4	63,986	53.6	23.3
	2007	1,107,147	923.3	6.6	1,031,351	860.1	5.9	75,796	63.2	17.9
	2008	1,178,856	977.5	5.9	1,089,152	903.1	5.0	89,704	74.4	17.7
	2009	1,233,475	1022.0	4.5	1,129,108	935.5	3.6	104,367	86.5	16.2
	2010	1,293,181	1068.8	4.6	1,170,995	967.9	3.5	122,186	101.0	16.8
	2011	1,360,766	1121.1	4.9	1,217,715	1003.2	3.7	143,051	117.9	16.7
	2012	1,410,697	1158.5	3.3	1,246,303	1023.5	2.0	164,394	135.0	14.5
	2013	1,434,650	1175.7	1.5	1,244,968	1020.3	-0.3	189,682	155.5	15.1
	2014	1,459,140	1193.0	1.5	1,245,642	1018.4	-0.2	213,498	174.6	12.3
	2015	1,470,071	1199.6	0.6	1,230,811	1004.3	-1.4	239,260	195.2	11.8
Percentage change (%) 2005 - 2015		45.3	40.7		28.2	24.1		363.4	348.7	
Spearman's r, p-value**		>.999, p<.001**	>.999, p<.001**		0.918, p<.001**	0.909 p<.001**		>.999, p<.001**	>.999, p<.001**	

B.4 Trends in prescribing by age

Increases in the number of people receiving opioid analgesic prescriptions were observed in all but the youngest age group over the period observed (Table B.8). When data was adjusted to age-group population, it was demonstrated people aged 65 years and over, had higher numbers of prescriptions issued than younger people (Figure B.8).

Table B.8: Trends in the number of people receiving opioid prescriptions stratified by age group

	Age-group											
	18 – 24		25 – 44		45 – 64		65 – 74		75 – 84		85+	
Year	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000
2005	17,555	65.4	89,804	116.3	150,091	196.9	76,472	281.1	53,982	291.2	18,374	294.8
2006	18,065	66.0	93,444	121.1	155,944	201.7	76,352	279.0	51,894	281.5	19,013	288.6
2007	19,604	70.0	102,151	132.4	169,499	216.3	80,038	288.4	53,639	292.3	20,091	291.8
2008	20,245	71.2	107,708	139.8	179,826	226.9	83,308	293.5	54,845	298.1	21,061	298.3
2009	21,098	73.1	111,133	145.0	187,579	234.4	86,308	296.7	56,213	304.6	21,515	298.3

2010	21,086	72.1	112,319	147.9	193,826	240.0	88,802	298.9	58,288	312.6	22,358	303.2
2011	20,990	70.9	114,367	151.6	199,636	245.1	91,595	302.6	60,253	319.9	23,030	305.7
2012	20,570	68.5	114,420	153.5	202,684	249.8	95,185	299.2	61,759	323.7	24,311	316.0
2013	19,779	66.3	112,348	151.3	200,999	247.9	97,203	295.0	62,869	324.3	24,685	319.3
2014	18,896	63.9	110,409	149.5	201,750	247.9	99,065	292.7	64,780	328.1	25,693	325.8
2015	17,763	60.6	107,077	145.2	200,222	245.4	100,641	290.8	65,267	327.4	25,859	326.1
Rate change (%)	1.2	-7.3	19.2	24.8	33.4	24.7	31.6	3.5	20.9	12.4	40.7	10.6
Spearman's r, p-value*	0.109, p=0.750	-0.300, p=0.370	0.582, p=0.060	0.782, p<0.05*	0.918, p<.001*	0.916, p<.001*	0.991, p<.001*	0.445, p=0.170	0.973, p<.001*	0.982, p<.001*	>.999, p<.001*	0.973, p<.001*

*p<0.05 = statistically significant

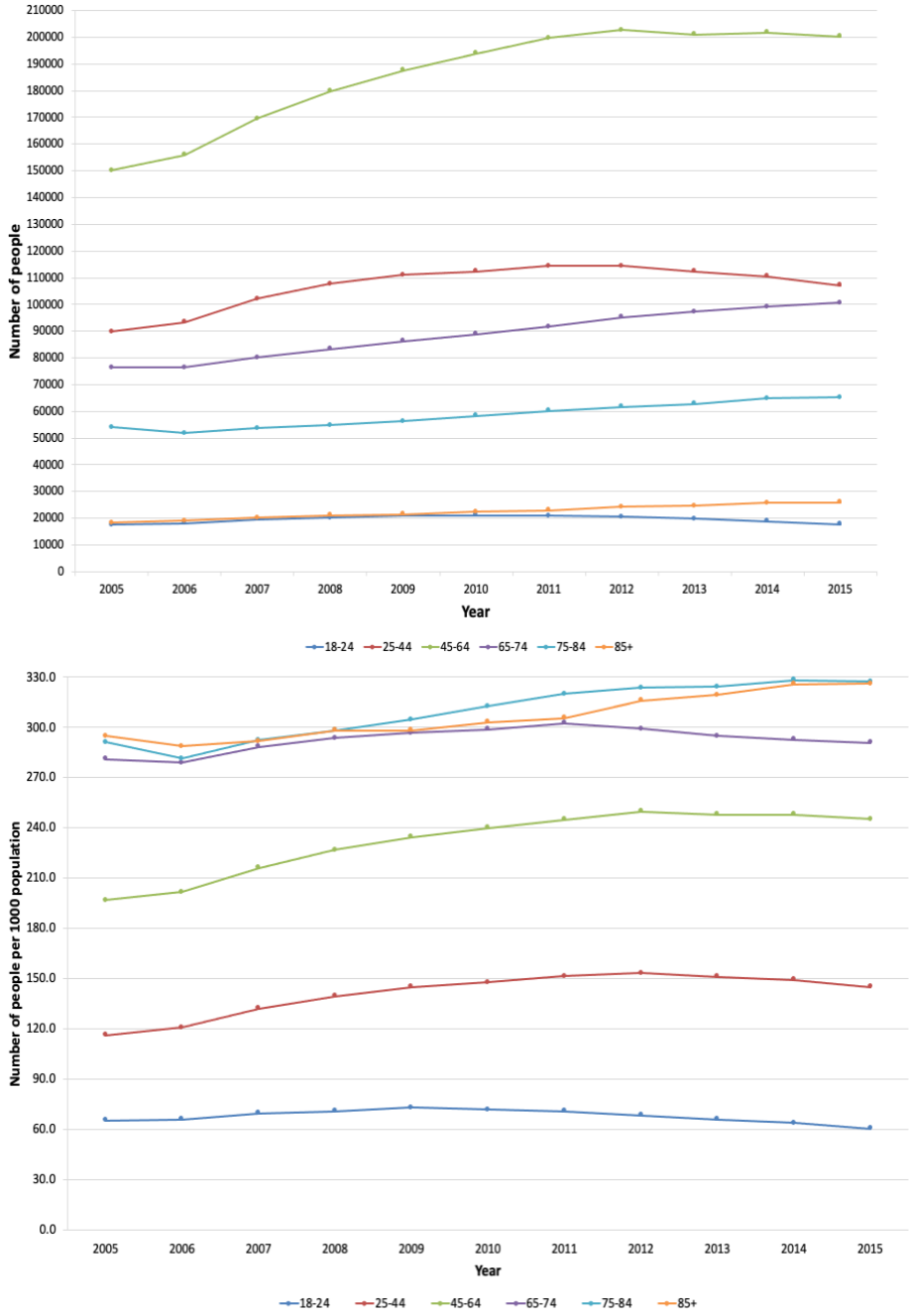


Figure B.8: Left: Trends in the number of people issued with opioid prescriptions between 2005 and 2015, stratified by age-group. Right: Data displayed by number of people per 1000 age-group adjusted population per year

The larger increases in numbers of people per 1000 population receiving prescriptions were of 24.8% (from 116.3 to 145.2 people per 1000 population, Spearman's r=0.782, p<0.05) in age 25 to 44 years and 24.7% (from 196.9 to 245.4 people per 1000 population, Spearman's r=0.916, p<.001) in 45- to 64-year-olds. Strong correlations, indicating an increasing trend over time, were noted in 4 age groups (Table B.8). A moderate increase was noted in the number of people aged 45 to 64 years. A reduction was observed in the number of people per 1000 population aged 18-to 24 years receiving opioid which had a weak correlation based on Spearman's r (Table B.8).

Kruskal-Wallis test output revealed a statistically significant difference in the number of people receiving opioid prescriptions over the study period (H=56.75, p<.001, η^2=0.86, d_{Cohen}= 5.01) . Dunn's pairwise comparisons and Bonferroni corrections confirmed significantly more people aged 65 years and over received prescriptions than those aged 18 to 24 years or 25 to 44 years. Significantly more people aged 85 years and over had prescriptions than those aged 45 to 64 years old. No statistical differences were noted in the remaining pairs compared (Table B.9 and Figure B.9).

Table B.9: Dunn's pairwise comparisons and Bonferroni correction output for people per 1000 population receiving opioid prescriptions, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	>.999				
45-64	0.094	>.999			
65-74	<.001*	<0.050*	0.684		
75-84	<.001*	<.001*	0.069	>.999	
85+	<.001*	<.001*	<0.050*	>.999	>.999

*p<0.05 = statistically significant

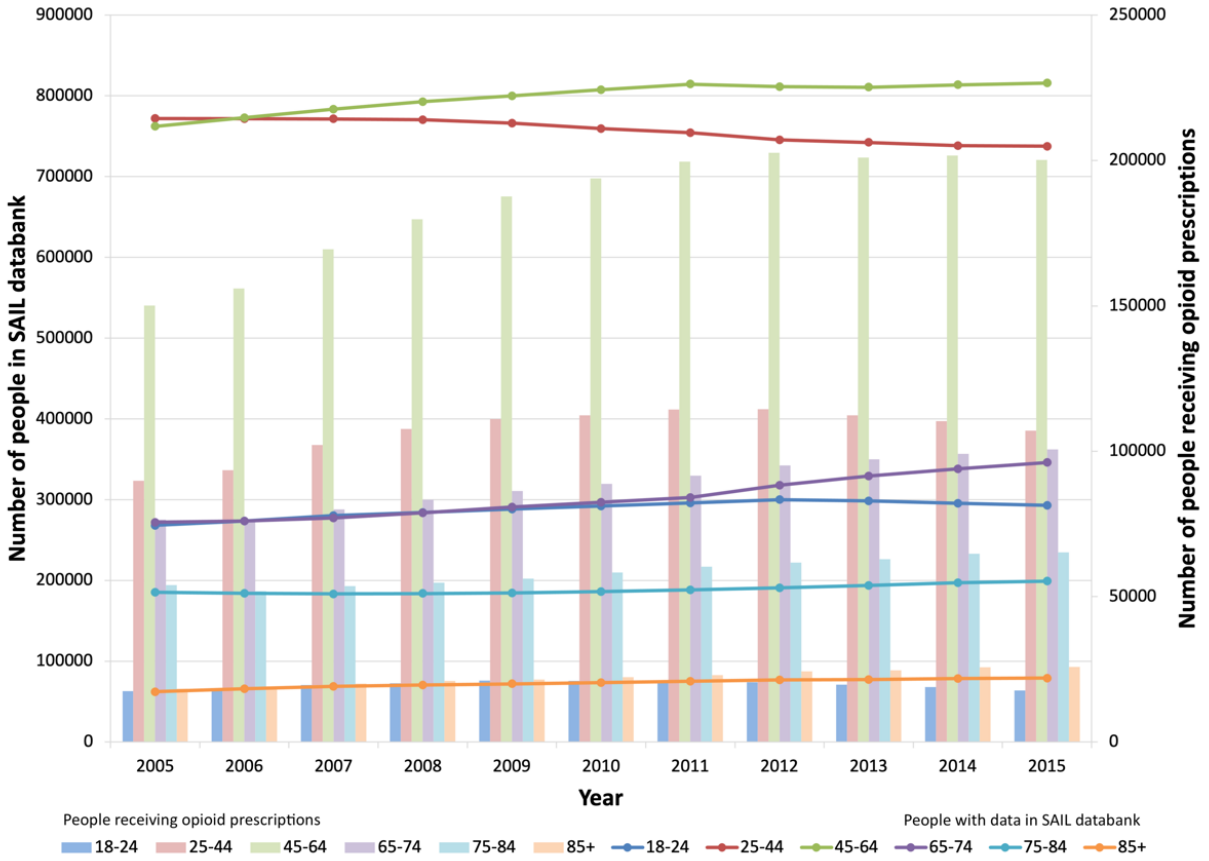


Figure B.9: Comparison of trends in population and number of people receiving opioid prescriptions based on SAIL databank populations 2005 to 2015

The trends in the number of people receiving weak opioid prescriptions between 2005 and 2015 varied, depending on the age-group examined (Figure B.10). The annual number of people receiving weak opioid prescriptions reduced in 3 of the 6 age-groups, which was in contrast to actual age-adjusted populations over the same time, when over the same time period, the only reduction in annual

number of people was in the 25-44 years age-group (Table B.10). There was a significant difference (Kruskal-Wallis H=57.73, p<.001, η^2=0.88, d_{Cohen}= 5.41) in the number of people receiving weak opioid prescriptions when the data was examined by age-group. As with previous pairwise comparisons, statistically more people age 65 years and over, were confirmed to receive weak opioid prescriptions when compared to people age 18-44 years. Statistically more people age 75-84 years, but not those age 65-74 or 85+ year received prescriptions when compared to the 45-64 years age-group (Table B.11).

The annual number of people in the 18 – 24 years age group reduced by 8.6% (from 64.4 to 58.9 people per 1000 age-adjusted population, Spearman's r= -0.364, p>0.05) between 2005 and 2015, despite an increase of 12% (from 64.4 to 72.1 people per 1000 age-adjusted population) from the start of the study to 2009 (**Error! Reference source not found.**).

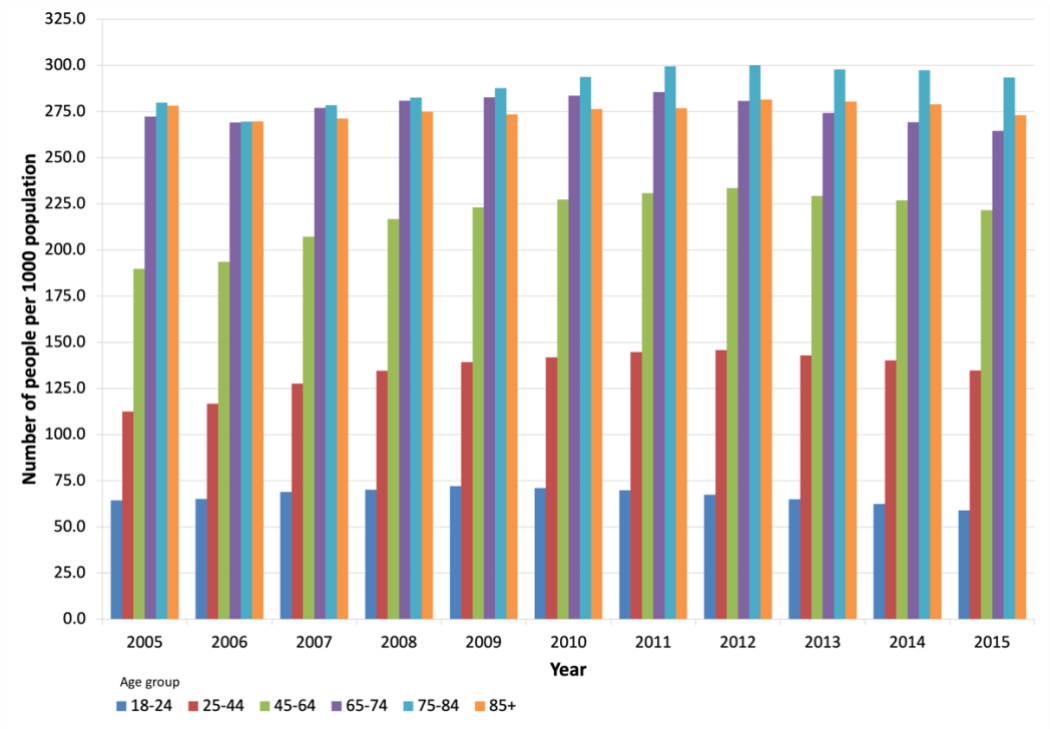


Figure B.10: Trends in number of people receiving weak opioid analgesic prescriptions, stratified by age group and adjusted to age-group population

Table B.10: Trends in the number of people receiving weak opioid prescriptions, stratified by age group

	Age-group											
	18 – 24		25 – 44		45 – 64		65 – 74		75 – 84		85+	
	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000
2005	17,287	64.4	86,835	112.5	144,712	189.8	74,085	272.3	51,873	279.8	17,337	278.2
2006	17,811	65.1	90,064	116.7	149,698	193.6	73,664	269.1	49,688	269.5	17,762	269.6
2007	19,327	69.0	98,417	127.6	162,404	207.2	76,864	277.0	51,116	278.5	18,671	271.1
2008	19,957	70.2	103,736	134.6	171,752	216.7	79,722	280.9	51,989	282.6	19,404	274.8
2009	20,799	72.1	106,736	139.3	178,496	223.1	82,258	282.8	53,104	287.7	19,733	273.6
2010	20,784	71.1	107,706	141.8	183,606	227.3	84,244	283.6	54,786	293.8	20,372	276.3
2011	20,683	69.9	109,239	144.8	188,023	230.8	86,452	285.6	56,411	299.5	20,857	276.9
2012	20,223	67.4	108,719	145.8	189,501	233.5	89,312	280.7	57,252	300.1	21,655	281.5
2013	19,399	65.0	106,116	142.9	185,901	229.3	90,361	274.2	57,737	297.9	21,680	280.5
2014	18,457	62.5	103,480	140.1	184,579	226.8	91,146	269.3	58,715	297.4	21,998	278.9
2015	17,256	58.9	99,401	134.8	180,833	221.6	91,567	264.6	58,511	293.5	21,652	273.0
Rate change (%)	-0.2	-8.6	14.5	19.8	25.0	16.8	23.6	-2.8	12.8	4.9	24.9	-1.8
Spearman's r, p-value*	0.018, p=0.60	-0.364, p=0.272	0.455, p=0.160	0.691, p<0.05*	0.782, p<0.05*	0.691, p<0.05*	0.991, p<.001*	-0.127, p=0.709	0.964, p<.001*	0.755, p<0.01*	0.945, p<.001*	0.418, p=0.201

*p<0.05 = statistically significant

Table B.11: Dunn's pairwise comparisons and Bonferroni correction output for people per 1000 population receiving weak opioid prescriptions, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	>.999				
45-64	0.108	>.999			
65-74	<.001*	<0.050*	0.799		
75-84	<.001*	<.001*	<0.050*	>.999	
85+	<.001*	<.001*	<0.050*	>.999	>.999

*p<0.05 = statistically significant

The greatest percentage increase in the number of people receiving weak opioid prescriptions, was of 19.8% (from 112.5 to 134.8 people per 1000 age-adjusted population, Spearman's r=0.691, p<0.05) in people aged 24 -44 years. There was a peak of 145.8 people per 1000 population in 2012 (29.6% increase) before the annual number of people in that age-group began to decline (Figure B.11).

The trends in the number of people receiving strong opioid prescriptions demonstrated large increases in all age-groups other than those aged 18 – 24 years (Table B.12), where the numbers increased 73.2 (from 1.0 to 1.7 people per 1000 population, Spearman's r=0.882, p<.001) (Table B.12).

The largest percentage increase in the annual number of people receiving strong opioid prescriptions was noted in the 45 – 64 years age-group. The 236.8% (from 7.1 to 23.8 people per 1000 age-adjusted population, Spearman's r=>.999, p<.001) increase, was fairly steady over the 11 years. However, from 2011, there was a faster rate of annual increase, notably in the age groups 65 years and above (Table B.12).

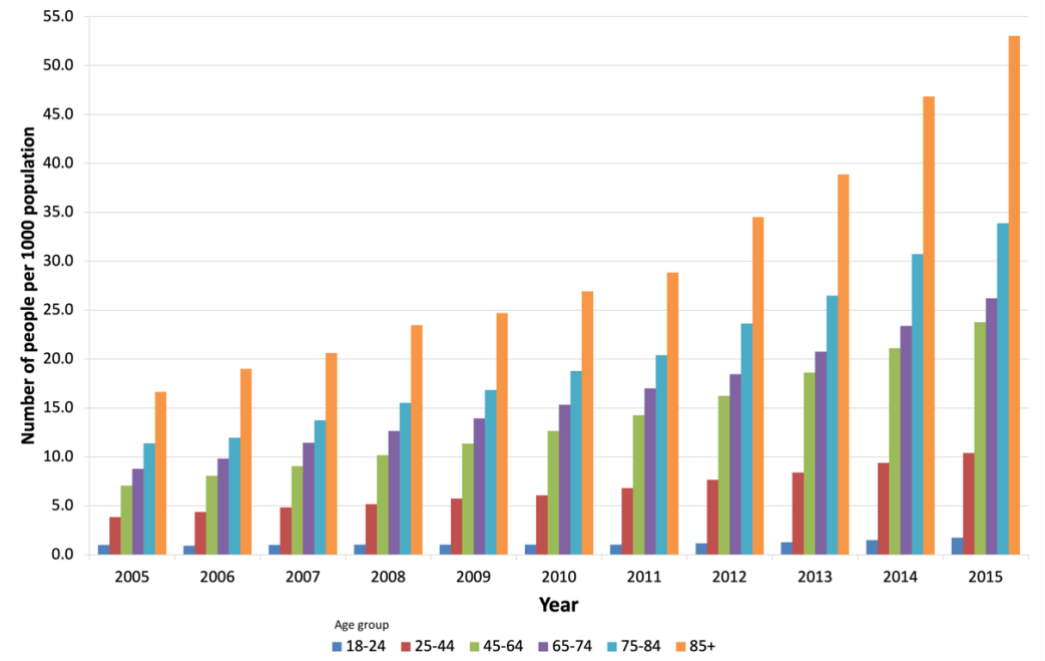


Figure B.11: Trends in the number of people receiving strong opioid prescriptions between 2005 and 2015 and stratified by age-group. Data adjusted to age-group adjusted population

The group with the highest number of people receiving strong opioid prescriptions was 85 years and over (Figure B.11). Based on median values, 43% more people aged 85 and above, were issued with strong opioid prescriptions than the number in the next highest recipients, aged 75 to 84 years (26.9 and 18.8 people per 1000 age-adjusted population respectively).

Very similar increases in the number of people receiving strong opioid prescriptions were noted in the 65 – 74 years age-group (198.8%, from 8.8 to 26.2 people per 1000 age-adjusted population) and the 75 – 84 years age-group (197.8%, from 11.4 to 33.9 people per 1000 age-adjusted population) (Table

B.12). More people in the older of the two groups were issued with prescriptions however, with 26% more people aged 74 – 84 years receiving prescriptions based on median values (223.3 versus 177.8 people per 1000 age-adjusted population respectively) (Table B.12).

Differences between all the groups were calculated to be statistically significant (Kruskal-Wallis H =37.84, $p<.001$, $\eta^2=0.55$, $d_{Cohen}= 2.20$). Pairwise comparisons confirmed significantly fewer people aged 18 to 25 years received opioid prescriptions than all age groups other than 25 to 44 years (Table B.13). There was also confirmation significantly fewer people aged 25 to 44 years, received opioids than people in the oldest age group. No other statistical differences were detected (Table B.13).

Table B.12: Trends in the number of people receiving strong opioid prescriptions, stratified by age group

Year	Age-group											
	18 – 24		25 – 44		45 – 64		65 – 74		75 – 84		85+	
	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000	Number of people	People per 1000
2005	268	1.0	2,969	3.8	5,379	7.1	2,387	8.8	2,109	11.4	1,037	16.6
2006	254	0.9	3,380	4.4	6,246	8.1	2,688	9.8	2,206	12.0	1,251	19.0
2007	277	1.0	3,734	4.8	7,095	9.1	3,174	11.4	2,523	13.7	1,420	20.6
2008	288	1.0	3,972	5.2	8,074	10.2	3,586	12.6	2,856	15.5	1,657	23.5
2009	299	1.0	4,397	5.7	9,083	11.4	4,050	13.9	3,109	16.8	1,782	24.7
2010	302	1.0	4,613	6.1	10,220	12.7	4,558	15.3	3,502	18.8	1,986	26.9
2011	307	1.0	5,128	6.8	11,613	14.3	5,143	17.0	3,842	20.4	2,173	28.8
2012	347	1.2	5,701	7.6	13,183	16.2	5,873	18.5	4,507	23.6	2,656	34.5
2013	380	1.3	6,232	8.4	15,098	18.6	6,842	20.8	5,132	26.5	3,005	38.9
2014	439	1.5	6,929	9.4	17,171	21.1	7,919	23.4	6,065	30.7	3,695	46.9
2015	507	1.7	7,676	10.4	19,389	23.8	9,074	26.2	6,756	33.9	4,207	53.1
Rate change (%)	89.2	73.2	158.5	170.6	260.5	236.8	280.1	198.8	220.3	197.8	305.7	218.8
Spearman's r, p-value*	0.991, p<.001*	0.882, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*

*p<0.05 = statistically significant

Table B.13: Dunn's pairwise comparisons and Bonferroni correction output for people per 1000 population receiving strong opioid prescriptions, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	0.373				
45-64	<0.005*	>.999			
65-74	<0.005*	>.999	>.999		
75-84	<.001*	0.442	>.999	>.999	
85+	<.001*	<0.050*	>.999	>.999	>.999

*p<0.05 = statistically significant

B.4.1 Trends in numbers of prescriptions by age-group

Table B.14: Trends in the total number of opioid prescriptions stratified by age group

	Age-group											
	18 – 24		25 – 44		45 – 64		65 – 74		75 – 84		85+	
Year	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000
2005	31,950	119.1	304,699	394.7	626,760	822.1	329,694	1211.8	235,612	1271.1	84,702	1359.1
2006	32,457	118.6	318,389	412.7	654,666	846.7	333,848	1219.7	229,671	1245.7	87,301	1325.3
2007	35,726	127.5	345,851	448.3	715,204	912.7	354,076	1275.9	238,786	1301.2	93,457	1357.2
2008	36,641	128.8	369,762	479.9	778,707	982.4	374,467	1319.4	247,010	1342.6	97,764	1384.7
2009	38,386	133.1	390,721	509.8	822,823	1028.3	390,644	1342.9	258,730	1401.8	101,247	1403.6
2010	38,761	132.6	407,964	537.1	872,388	1080.0	409,914	1379.9	272,934	1463.7	106,611	1445.9
2011	39,955	135.0	432,110	572.7	926,426	1137.3	429,556	1419.1	285,696	1516.8	113,294	1503.9
2012	40,162	133.8	443,172	594.4	962,289	1185.8	454,683	1429.2	297,987	1561.7	120,114	1561.3
2013	39,055	130.9	443,657	597.6	976,109	1204.0	470,904	1429.2	305,635	1576.7	123,346	1595.7
2014	38,466	130.2	440,743	596.8	994,740	1222.5	483,118	1427.5	315,598	1598.5	126,053	1598.3
2015	36,275	123.8	441,430	598.5	1,002,718	1229.0	491,974	1421.5	318,235	1596.2	124,742	1573.0
Rate change (%)	13.5	4.0	44.9	51.6	60.0	49.5	49.2	17.3	35.1	25.6	47.3	15.7
Spearman's r, p-value*	0.627, p<0.05*	0.418, p=0.201	0.927, p<.001*	0.991, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	0.909, p<.001*	0.991, p<.001*	0.982, p<.001*	0.991, p<.001*	0.945, p<.001*

Rx = prescriptions *p<0.05 = statistically significant

Table B.15: Dunn's pairwise comparisons and Bonferroni correction output for all opioid prescriptions per 1000 population, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	>.999				
45-64	0.108	>.999			
65-74	<.001*	<0.050	0.820		
75-84	<.001*	.001*	<0.050*	>.999	
85+	<.001*	<.001*	<0.050*	>.999	>.999

*p<0.050=statistically significant

Table B.16: Trends in the number of weak opioid prescriptions, stratified by age group

	Age-group											
	18 – 24		25 – 44		45 – 64		65 – 74		75 – 84		85+	
Year	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000
2005	29,766	110.9	279,581	362.2	589,893	773.8	316,152	1162.1	224,977	1213.7	80,072	1284.8
2006	30,275	110.6	287,318	372.4	610,343	789.4	317,689	1160.7	217,872	1181.7	81,095	1231.0
2007	33,436	119.3	311,769	404.1	661,935	844.7	334,453	1205.2	224,313	1222.3	86,068	1249.9
2008	34,136	120.0	331,408	430.1	714,588	901.5	351,318	1237.8	230,592	1253.3	89,181	1263.2
2009	36,045	124.9	348,405	454.6	747,893	934.7	364,008	1251.4	240,223	1301.5	91,556	1269.2
2010	36,467	124.7	358,869	472.5	785,957	973.0	378,349	1273.7	250,777	1344.9	95,656	1297.3
2011	37,673	127.3	375,571	497.8	823,998	1011.6	392,528	1296.7	260,365	1382.3	100,064	1328.3
2012	37,840	126.0	379,447	509.0	843,144	1039.0	411,095	1292.2	267,238	1400.6	104,483	1358.1
2013	36,816	123.4	374,078	503.9	837,467	1033.0	419,585	1273.4	270,753	1396.8	106,111	1372.8
2014	35,789	121.1	368,118	498.5	836,574	1028.1	425,053	1255.9	276,218	1399.0	106,274	1347.5
2015	33,447	114.2	361,235	489.8	824,065	1010.1	425,647	1229.8	274,092	1374.8	103,191	1301.3
Rate change (%)	12.4	2.9	29.2	35.2	39.7	30.5	34.6	5.8	21.8	13.3	28.9	1.3
Spearman's r, p-value*	0.582, p=0.60	0.418, p=0.201	0.827, p<0.01*	0.873, p<.001*	0.909, p<.001*	0.873, p<.001*	>.999, p<.001*	0.582, p=0.060	0.964, p<.001*	0.873, p<.001*	0.945, p<.001*	0.791, p<0.01*

Rx = prescriptions *p<0.05 = statistically significant

Table B.17: Dunn's pairwise comparisons and Bonferroni correction output for weak opioid prescriptions per 1000 population, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	>.999				
45-64	0.108	>.999			
65-74	<.001*	<0.010*	0.318		
75-84	<.001*	<.001*	<0.010*	>.999	
85+	<.001*	<0.010*	0.495	>.999	>.999

*p<0.05 = statistically significant

Table B.18: Trends in the number strong opioid prescriptions, stratified by age group

	Age-group											
	18 – 24		25 – 44		45 – 64		65 – 74		75 – 84		85+	
	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000	Number of Rx	Rx per 1000
2005	2,184	8.1	25,118	32.5	36,867	48.4	13,542	49.8	10,635	57.4	4,630	74.3
2006	2,182	8.0	31,071	40.3	44,323	57.3	16,159	59.0	11,799	64.0	6,206	94.2
2007	2,290	8.2	34,082	44.2	53,269	68.0	19,623	70.7	14,473	78.9	7,389	107.3
2008	2,505	8.8	38,354	49.8	64,119	80.9	23,149	81.6	16,418	89.2	8,583	121.6
2009	2,341	8.1	42,316	55.2	74,930	93.6	26,636	91.6	18,507	100.3	9,691	134.3
2010	2,294	7.8	49,095	64.6	86,431	107.0	31,565	106.3	22,157	118.8	10,955	148.6
2011	2,282	7.7	56,539	74.9	102,428	125.7	37,028	122.3	25,331	134.5	13,230	175.6
2012	2,322	7.7	63,725	85.5	119,145	146.8	43,588	137.0	30,749	161.2	15,631	203.2
2013	2,239	7.5	69,579	93.7	138,642	171.0	51,319	155.8	34,882	180.0	17,235	223.0
2014	2,677	9.1	72,625	98.3	158,166	194.4	58,065	171.6	39,380	199.5	19,779	250.8
2015	2,828	9.7	80,195	108.7	178,653	219.0	66,327	191.6	44,143	221.4	21,551	271.8
Rate change (%)	29.5	18.6	219.3	234.1	384.6	352.8	389.8	285.0	315.1	285.9	365.5	265.8
Spearman's r, p-value*	0.609, p<0.05*	0.041, p=0.905	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*	>.999, p<.001*

Rx = prescriptions *p<0.05 = statistically significant

Table B.19: Dunn's pairwise comparisons and Bonferroni correction output for strong opioid prescriptions per 1000 population, stratified by age-group

Age group (years)	**18-24**	**25-44**	**45-64**	**65-74**	**75-84**
25-44	>.999				
45-64	<0.010*	0.630			
65-74	<0.005*	0.149	>.999		
75-84	<.001*	<0.050*	>.999	>.999	
85+	<.001*	<.001*	0.115	0.507	>.999

*p<0.05 = statistically significant

Appendix C Trends in prescribing by socioeconomic deprivation

C.1 Data preparation

Table C.1: Example of LSOA data used to determine Health Board WIMD population estimates

LSOA	National Rank	LSOA number	County	Population estimate
W01000001: Aberffraw & Rhosneigr 1	731	W01000001	Isle of Anglesey 007A	1,113
W01000002: Aberffraw & Rhosneigr 2	852	W01000002	Isle of Anglesey 007B	1,266
W01000003: Amlwch Port	527	W01000003	Isle of Anglesey 001A	2,519
W01000004: Amlwch Rural	768	W01000004	Isle of Anglesey 001B	1,281
W01000005: Beaumaris	1,032	W01000005	Isle of Anglesey 005A	1,936
W01000006: Bodffordd	917	W01000006	Isle of Anglesey 006A	1,534
W01000007: Bodorgan	870	W01000007	Isle of Anglesey 009A	1,696
W01000008: Braint	1,811	W01000008	Isle of Anglesey 008A	1,522
W01000009: Bryngwran	486	W01000009	Isle of Anglesey 007C	1,908
W01000010: Brynteg	1,500	W01000010	Isle of Anglesey 002A	1,868
W01000011: Cadnant (Isle of Anglesey)	1,602	W01000011	Isle of Anglesey 008B	1,229
W01000012: Cefni	1,649	W01000012	Isle of Anglesey 006B	1,487
W01000013: Cwm Cadnant	1,651	W01000013	Isle of Anglesey 005B	2,260
W01000014: Cyngar	1,115	W01000014	Isle of Anglesey 006C	2,062
W01000015: Gwyngyll	1,758	W01000015	Isle of Anglesey 008C	1,581
W01000016: Holyhead Town	246	W01000016	Isle of Anglesey 003A	1,201
W01000017: Kingsland	377	W01000017	Isle of Anglesey 003B	1,532
W01000018: Llanbadrig	890	W01000018	Isle of Anglesey 001C	1,358
W01000019: Llanbedrgoch	1,318	W01000019	Isle of Anglesey 005C	1,505
W01000020: Llanddyfnan	1,335	W01000020	Isle of Anglesey 002B	1,314
W01000021: Llaneilian	826	W01000021	Isle of Anglesey 002C	2,262
W01000022: Llanfaethlu	953	W01000022	Isle of Anglesey 004A	1,650
W01000023: Llanfair-yn-Neubwll 1	878	W01000023	Isle of Anglesey 007D	1,411
W01000024: Llanfair-yn-Neubwll 2	1,058	W01000024	Isle of Anglesey 007E	1,606
W01000025: Llanfihangel Ysgeifiog	1,121	W01000025	Isle of Anglesey 009B	2,025
W01000026: Llangoed	986	W01000026	Isle of Anglesey 005D	1,226
W01000027: Llanidan	736	W01000027	Isle of Anglesey 009C	1,849
W01000028: Llannerch-y-medd	644	W01000028	Isle of Anglesey 001D	1,947
W01000029: London Road	341	W01000029	Isle of Anglesey 003C	1,499
W01000030: Maeshyfryd	320	W01000030	Isle of Anglesey 003D	2,306
W01000031: Mechell	773	W01000031	Isle of Anglesey 001E	1,551
W01000032: Moelfre	932	W01000032	Isle of Anglesey 002D	1,063
W01000033: Morawelon	146	W01000033	Isle of Anglesey 003E	1,507
W01000034: Parc a'r Mynydd	1,066	W01000034	Isle of Anglesey 004B	1,156
W01000097: Ogwen 2	765	W01000097	Gwynedd 003D	1,107
W01000098: Peblig (Caernarfon)	119	W01000098	Gwynedd 006C	2,300
W01000099: Penisarwaun	1,321	W01000099	Gwynedd 005C	1,762
W01000100: Penrhyndeudraeth 1	1,194	W01000100	Gwynedd 010B	1,057
W01000101: Penrhyndeudraeth 2	1,347	W01000101	Gwynedd 013D	1,530
W01000918: Crynant	991	W01000918	Neath Port Talbot 002A	1,906
W01000919: Cwmllynfell	716	W01000919	Neath Port Talbot 020A	1,175
W01000920: Cymmer (Neath Port Talbot) 1	446	W01000920	Neath Port Talbot 011A	1,254
W01000921: Cymmer (Neath Port Talbot) 2	25	W01000921	Neath Port Talbot 011B	1,574

W01000922: Dyffryn 1	551	W01000922	Neath Port Talbot 007C	1,687
W01000923: Dyffryn 2	1,315	W01000923	Neath Port Talbot 007D	1,475
W01000924: Glyncorrwg	168	W01000924	Neath Port Talbot 011C	1,100
W01000925: Glynneath 1	268	W01000925	Neath Port Talbot 003B	1,565
W01000926: Glynneath 2	1,160	W01000926	Neath Port Talbot 003C	1,860
W01000927: Godre'r graig	642	W01000927	Neath Port Talbot 020B	1,655
W01000928: Gwaun-Cae-Gurwen 1	497	W01000928	Neath Port Talbot 020C	1,602
W01000929: Gwaun-Cae-Gurwen 2	475	W01000929	Neath Port Talbot 020D	1,299
W01000930: Gwynfi	193	W01000930	Neath Port Talbot 011D	1,365
W01000931: Lower Brynamman	627	W01000931	Neath Port Talbot 020E	1,332
W01000932: Margam 1	583	W01000932	Neath Port Talbot 019A	1,044
W01000933: Margam 2	1,429	W01000933	Neath Port Talbot 019B	1,981
W01000934: Neath East 1	167	W01000934	Neath Port Talbot 008A	1,263
W01000935: Neath East 2	141	W01000935	Neath Port Talbot 008B	1,572
W01000936: Neath East 3	201	W01000936	Neath Port Talbot 012A	1,525
W01000937: Neath East 4	196	W01000937	Neath Port Talbot 013E	2,057
W01000938: Neath North 1	1,465	W01000938	Neath Port Talbot 008C	1,390
W01000939: Neath North 2	92	W01000939	Neath Port Talbot 008D	1,262
W01000940: Neath North 3	271	W01000940	Neath Port Talbot 008E	1,291
W01000941: Neath South 1	364	W01000941	Neath Port Talbot 012B	1,545
W01000942: Neath South 2	176	W01000942	Neath Port Talbot 012C	1,891
W01000943: Neath South 3	1,765	W01000943	Neath Port Talbot 012D	1,555

Using WIMD2011 data (StatsWales 2010)

Table C.2: Welsh Country population data for 2011. Designated Health Board indicated

County code	County	Estimated population	Health Board
W06000001	Ise of Anglesey / Ynys Mon	69,913	BCUHB
W06000002	Gwynedd / Gwynedd	121,523	BCUHB
W06000003	Conwy /Conwy	115,326	BCUHB
W06000004	Denbighshire / Sir Ddinbych	93,919	BCUHB
W06000005	Flintshire / Sir y Fflint	152,666	BCUHB
W06000006	Wrexham / Wrecsam	135,070	BCUHB
W06000008	Ceredigion / Ceredigion	75,293	HDUHB
W06000009	Pembrokeshire / Sir Benfro	122,613	HDUHB
W06000010	Carmarthenshire / Sir Gaerfyrddin	183,961	HDUHB
W06000011	Swansea / Abertawe	238,691	ABMUHB
W06000012	Neath Port Talbot / Castell-nedd Port Talbot	139,880	ABMUHB
W06000013	Bridgend / Pen-y-bont ar Ogwr	139,410	ABMUHB
W06000014	The Vale of Glamorgan / Bro Morgannwg	126,679	CVUHB
W06000015	Cardiff / Caerdydd	345,442	CVUHB
W06000016	Rhondda Cynon Taf / Rhondda Cynon Taf	234,373	CTUHB
W06000018	Caerphilly / Caerffili	178,782	CTUHB
W06000019	Blaenau Gwent / Blaenau Gwent	69,812	ABUHB
W06000020	Torfaen / Tor-faen	91,190	ABUHB

W06000021	Monmouthshire / Sir Fynwy	91,508	ABUHB
W06000022	Newport / Casnewydd	145,785	ABUHB
W06000023	Powys / Powys	133,071	PTHB
W06000024	Merthyr Tydfil / Merthyr Tudful	58,851	CTUHB
	Total population	3,063,758	

(StatsWales 2010)

Table C.3: Population calculations for each Health Board using mid-year estimates and adjusted to SAIL percentage representation per Health Board

	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB	Total Welsh population
%of total	17%	19%	22%	16%	10%	12%	4%	
2005	504,781	564,167	653,246	475,088	296,930	356316	118772	2,969,300
2006	507,569	567,283	656,854	477,712	298,570	358284	119428	2,985,700
2007	511,071	571,197	661,386	481,008	300,630	360756	120252	3,006,300
2008	514,403	574,921	665,698	484,144	302,590	363108	121036	3,025,900
2009	512,921	572,518	684,575	463,818	292,899	379,051	133,090	3,038,872
2010	515,420	574,778	685,911	467,837	292,952	380,195	132,878	3,049,971
2011	517,981	577,077	688,417	472,121	293,224	381,867	133,071	3,063,758
2012	519,481	577,981	690,434	475,324	294,497	383,398	132,952	3,074,067
2013	520,710	579,101	691,986	478,869	295,135	383,906	132,705	3,082,412
2014	523,001	580,401	694,038	481,979	295,953	383,989	132,675	3,092,036
2015	525,466	581,789	694,473	484,752	296,735	383,229	132,642	3,099,086

SAIL population	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB	Total
2005	484,590	394,917	489,935	380,070	228,636	288,616	48,697	2,315,460
2006	487,266	397,098	492,641	382,170	229,899	290,210	48,965	2,328,249
2007	490,628	399,838	496,040	384,806	231,485	292,212	49,303	2,344,313
2008	493,827	402,445	499,274	387,315	232,994	294,117	49,625	2,359,597
2009	492,404	400,763	513,431	371,054	225,532	307,031	54,567	2,364,783
2010	494,803	402,345	514,433	374,270	225,573	307,958	54,480	2,373,862
2011	497,262	403,954	516,313	377,697	225,782	309,312	54,559	2,384,879
2012	498,702	404,587	517,826	380,259	226,763	310,552	54,510	2,393,199
2013	499,882	405,371	518,990	383,095	227,254	310,964	54,409	2,399,964
2014	502,081	406,281	520,529	385,583	227,884	311,031	54,397	2,407,785
2015	504,447	407,252	520,855	387,802	228,486	310,415	54,383	2,413,641

(StatsWales 2010)

Table C.4: Estimated populations per 1000 WIMD quintile per Health Board and total for Wales based on SAIL population estimates

ALLWales	WIMD 1	WIMD 2	WIMD 3	WIMD 4	WIMD 5
2005	474.3	471.9	449.2	439.0	478.2
2006	476.9	474.5	451.6	441.4	480.8
2007	480.2	477.8	454.8	444.5	484.2
2008	483.4	480.9	457.7	447.4	487.3
2009	479.4	481.3	462.9	454.1	484.6
2010	481.4	482.9	464.4	455.6	486.9
2011	483.7	484.9	466.5	457.6	489.6
2012	485.4	486. 6	468.0	459.1	491.5
2013	486.9	488.0	469.1	460.2	493.3
2014	488.7	489.3	470.4	461.5	495.2
2015	490.3	490.5	471.2	462.3	496.7

CTLHB	WIMD 1	WIMD 2	WIMD 3	WIMD 4	WIMD 5
2005	68.6	80.0	34.3	18.3	27.4
2006	69.0	80.5	34.5	18.4	27.6
2007	69.4	81.0	34.7	18.5	27.8
2008	69.9	81.5	34.9	18.6	28.0
2009	67.7	78.9	33.8	18.0	27.1
2010	67.7	79.0	33.8	18.0	27.1
2011	67.7	79.0	33.9	18.1	27.1
2012	68.0	79.4	34.0	18.1	27.2
2013	68.2	79.5	34.1	18.2	27.3
2014	68.4	79.8	34.2	18.2	27.3
2015	68.5	80.0	34.3	18.3	27.4

ABLHB	WIMD 1	WIMD 2	WIMD 3	WIMD 4	WIMD 5
2005	102.7	86.9	75.0	55.3	71.1
2006	103.2	87.4	75.4	55.6	71.5
2007	104.0	88.0	76.0	56.0	72.0
2008	104.6	88.5	76.5	56.3	72.4
2009	104.2	88.2	76.1	56.1	72.1
2010	104.6	88.5	76.4	56.3	72.4
2011	105.0	88.9	76.8	56.6	72.7
2012	105.2	89.0	76.9	56.6	72.8
2013	105.4	89.2	77.0	56.8	73.0
2014	105.6	89.4	77.2	56.9	73.1

HDLHB	WIMD 1	WIMD 2	WIMD 3	WIMD 4	WIMD 5
2005	20.2	54.8	98.1	72.2	43.3
2006	20.3	55.1	98.7	72.6	43.5
2007	20.5	55.5	99.4	73.1	43.8
2008	20.6	55.9	100.0	73.5	44.1
2009	21.5	58.3	104.4	76.8	46.1
2010	21.6	58.5	104.7	77.0	46.2
2011	21.7	58.8	105.2	77.3	46.4
2012	21.7	59.0	105.6	77.6	46.6
2013	21.8	59.1	105.7	77.7	46.6
2014	21.8	59.1	105.8	77.8	46.7

2015	105.9	89.6	77.4	57.0	73.3	**2015**	21.7	59.0	105.5	77.6	46.6

ABMUHB	**WIMD 1**	**WIMD 2**	**WIMD 3**	**WIMD 4**	**WIMD 5**	**PTHB**	**WIMD 1**	**WIMD 2**	**WIMD 3**	**WIMD 4**	**WIMD 5**
2005	126.0	106.6	72.7	63.0	116.3	**2005**	1.9	4.9	10.7	26.3	4.9
2006	126.7	107.2	73.1	63.3	116.9	**2006**	2.0	4.9	10.8	26.4	4.9
2007	127.6	107.9	73.6	63.8	117.8	**2007**	2.0	4.9	10.8	26.6	4.9
2008	128.4	108.6	74.1	64.2	118.5	**2008**	2.0	5.0	10.9	26.8	5.0
2009	128.0	108.3	73.9	64.0	118.2	**2009**	2.2	5.5	12.0	29.5	5.5
2010	128.6	108.9	74.2	64.3	118.8	**2010**	2.2	5.4	12.0	29.4	5.4
2011	129.3	109.4	74.6	64.6	119.3	**2011**	2.2	5.5	12.0	29.5	5.5
2012	129.7	109.7	74.8	64.8	119.7	**2012**	2.2	5.5	12.0	29.4	5.5
2013	130.0	110.0	75.0	65.0	120.0	**2013**	2.2	5.4	12.0	29.4	5.4
2014	130.5	110.5	75.3	65.3	120.5	**2014**	2.2	5.4	12.0	29.4	5.4
2015	131.2	111.0	75.7	65.6	121.1	**2015**	2.2	5.4	12.0	29.4	5.4

BCUHB	**WIMD 1**	**WIMD 2**	**WIMD 3**	**WIMD 4**	**WIMD 5**	**CVUHB**	**WIMD 1**	**WIMD 2**	**WIMD 3**	**WIMD 4**	**WIMD 5**
2005	63.7	93.1	112.7	147.0	78.4	**2005**	91.2	45.6	45.6	57.0	136.8
2006	64.0	93.6	113.3	147.8	78.8	**2006**	91.7	45.9	45.9	57.3	137.6
2007	64.5	94.2	114.1	148.8	79.4	**2007**	92.4	46.2	46.2	57.7	138.5
2008	64.9	94.9	114.8	149.8	79.9	**2008**	93.0	46.5	46.5	58.1	139.4
2009	66.7	97.6	118.1	154.0	82.1	**2009**	89.1	44.5	44.5	55.7	133.6
2010	66.9	97.7	118.3	154.3	82.3	**2010**	89.8	44.9	44.9	56.1	134.7
2011	67.1	98.1	118.8	154.9	82.6	**2011**	90.6	45.3	45.3	56.7	136.0
2012	67.3	98.4	119.1	155.3	82.9	**2012**	91.3	45.6	45.6	57.0	136.9
2013	67.5	98.6	119.4	155.7	83.0	**2013**	91.9	46.0	46.0	57.5	137.9
2014	67.7	98.9	119.7	156.2	83.3	**2014**	92.5	46.3	46.3	57.8	138.8
2015	67.7	99.0	119.8	156.3	83.3	**2015**	93.1	46.5	46.5	58.2	139.6

C.2 Results

C.2.1 Trends in the number of people receiving prescriptions by deprivation

Over the study period, 1.7 times more people in WIMD1 (most deprived) quintiles across Wales, received prescriptions for opioid analgesics than those in WIMD5 (least deprived) quintiles (Figure C.1). Greater percentage increases in the annual number of people receiving prescriptions, were observed in the less socio-economic deprived quintiles, the largest being in WIMD4 areas (28.7% increase, from 98.8 to 120.8 people per 1000 population). Spearman's r tests revealed strong correlations between time and the number of people receiving prescriptions, for all quintiles (Table C.5).

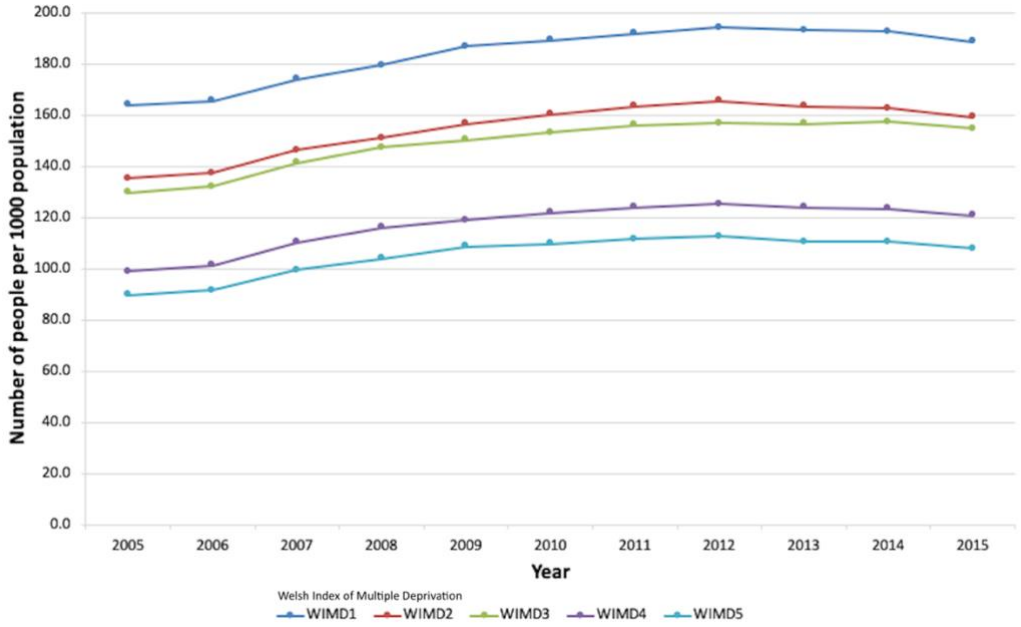


Figure C.1: Trends in the annual number of people receiving any opioid prescriptions presented by deprivation area and adjusted to population of each area of deprivation in Wales (WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most socio-economically deprived and WIMD5 = least socio-economically deprived)

There was little difference between patient numbers in the 2nd and 3rd quintiles, which narrowed in the final two years of the examination and was confirmed by statistical analysis (Figure C.1).

Comparison of the number of people living in each quintile over the study period demonstrated significantly more received opioid prescriptions as deprivation increased ($p<.001$, $\eta^2=0.883$, $d_{Cohen}=5.494$) (Table C.5). Pairwise comparison confirmed significantly more people in WIMD1-3 quintiles received prescriptions compared to the least deprived (WIMD5) ($p<.001$, $p<.001$ and $p<0.01$ respectively) (Table C.7). Statistically more people living in WIMD1 and WIMD2 areas received prescriptions when compared to the number in WIMD4 quintiles ($p<.001$ and $p<0.05$ respectively). Empirically greater numbers of people living in the most deprived quintiles received opioid prescriptions than any other quintile for the duration of the study. However, the difference in numbers between WIMD1, WIMD2 and WIMD3 were not confirmed to be statistically significant (Table C.7).

Table C.5: Annual number of people receiving opioid prescriptions per socio-economic deprivation quintile between 2005 -2015

	Number of people				
Year	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	77,785	63,835	58,211	43,386	42,861
2006	78,989	65,228	59,633	44,728	43,963
2007	83,539	69,836	64,206	48,987	48,145
2008	86,800	72,643	67,392	51,919	50,608
2009	89,502	75,331	69,589	53,993	52,683
2010	91,047	77,406	71,150	55,442	53,472
2011	92,810	79,297	72,837	56,674	54,655
2012	94,293	80,532	73,435	57,535	55,398
2013	94,037	79,771	73,439	57,073	54,516

2014	94,091	79,541	73,957	56,887	54,750
2015	92,541	78,122	72,911	55,852	53,618
Change rate (%) 2005-2015	19.0	22.4	25.3	28.7	25.1
Spearman's r, p-value	0.827, p<0.010*	0.793, p<0.010*	0.900, <.001*	0.800, p<0.010*	0.736, p<0.050*

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most socio-economically deprived, WIMD5 = least socio-economically deprived. *p-value <0.05 = statistically significant

Across the whole study period, 26.4% (975,434 n=3,700,881) of all people who received any opioid prescription were living in the most deprived areas of Wales (WIMD1). Conversely, people living in the least deprived areas comprised 15.3% (564,669) of people who received opioid prescriptions. In all areas, there was a peak in the annual number of people receiving prescriptions in 2012 with subsequent reductions over the three years that followed (Figure C.2).

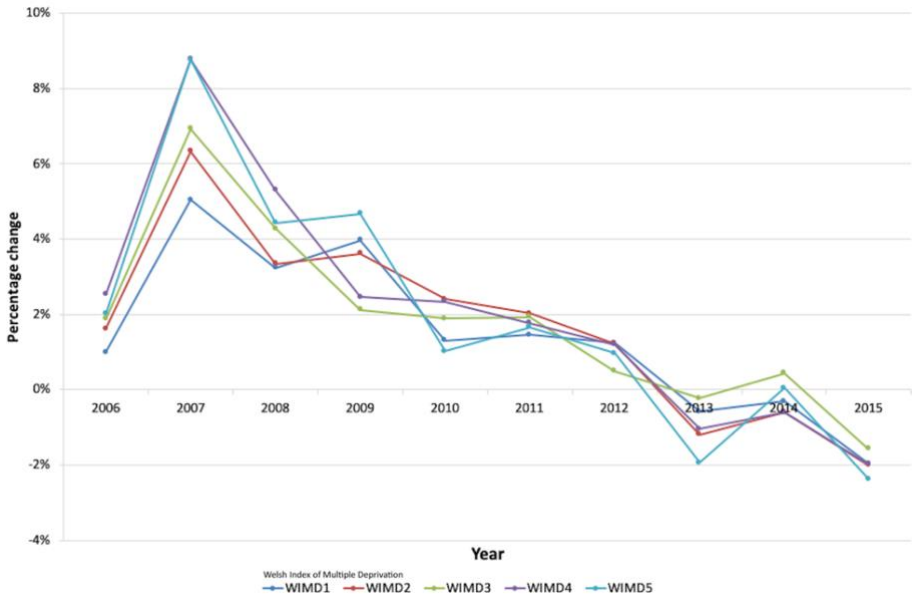


Figure C.2: Annual percentage change in the number of people prescribed opioids by quintiles of deprivation in Wales (WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived)

Table C.6: Comparison of quintile-population adjusted numbers of people receiving prescriptions for all opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015

	Number of people per 1000 population				
Year	**WIMD1**	**WIMD2**	**WIMD3**	**WIMD4**	**WIMD5**
2005	164.0	135.3	129.6	98.8	89.6
2006	165.6	137.5	132.0	101.3	91.4
2007	174.0	146.2	141.2	110.2	99.4
2008	179.6	151.1	147.2	116.0	103.9
2009	186.7	156.5	150.4	118.9	108.7
2010	189.1	160.3	153.2	121.7	109.8
2011	191.9	163.5	156.2	123.9	111.6
2012	194.3	165.5	156.9	125.3	112.7
2013	193.1	163.5	156.5	124.0	110.5
2014	192.5	162.6	157.2	123.3	110.6
2015	188.7	159.3	154.7	120.8	107.9
Change rate (%) 2005 - 2015	19.0	22.4	25.3	28.7	25.1

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most socio-economically deprived, WIMD5 = least socio-economically deprived. *p-value <0.05 = statistically significant

Table C.7: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number people receiving opioid prescriptions in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	.404			
3	.061	>.999		
4	<.001*	.023*	.188	
5	<.001*	<.001*	.007*	>.999

**p <0.05 = statistically significant. WIMD1=most socio-economically deprived, WIMD5=least socio-economically deprived*

Table C.8: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number people per 1000 population receiving opioid prescriptions in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	.813			
3	.064	>.999		
4	<.001*	.005*	.128	
5	<.001*	<.001*	.020*	>.999

**p <0.05 = statistically significant. WIMD1=most socio-economically deprived, WIMD5=least socio-economically deprived*

C.2.2 Trends in number of people receiving prescriptions by opioid-type

Examining prescribing trends by different opioid types, there were differences in the patterns of people receiving weak and strong opioid prescriptions, although the proportions of people within each area of deprivation were similar in all groups (Table C.9). However, the proportion of total weak opioid prescribing that was for people in the most deprived areas decreased by 3.1% between 2005 and 2015 (from 26.6% to 25.8% of people receiving weak opioids). The proportion of people in the most deprived areas of Wales receiving strong opioids however, increased by 5% over the same time.

Table C.9: Annual number of people receiving opioid prescriptions per socio-economic deprivation quintile and opioid-type between 2005 -2015

Year	Weak opioids					Strong opioids				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	75271	61630	56015	41750	41383	2514	2205	2196	1636	1478
2006	76255	62794	57218	42832	42284	2734	2434	2415	1896	1679
2007	80465	67039	61567	46874	46246	3074	2797	2639	2113	1899
2008	83323	69693	64458	49592	48503	3477	2950	2934	2327	2105
2009	85643	72055	66311	51363	50423	3859	3276	3278	2630	2260
2010	86849	73784	67570	52571	51115	4198	3622	3580	2871	2357
2011	88056	75269	68899	53573	51974	4754	4028	3938	3101	2681
2012	88921	75912	68953	53956	52318	5372	4620	4482	3579	3080
2013	87847	74559	68274	53129	51073	6190	5212	5165	3944	3443
2014	86969	73404	67987	52282	50860	7122	6137	5970	4605	3890
2015	84443	71248	66173	50830	49311	8098	6874	6738	5022	4307
Change rate (%) 2005-2015	12.2	15.6	18.1	21.7	19.2	222.1	211.7	206.8	207.0	191.4

WIMD=Welsh Index of Multiple Deprivation, WIMD1=most deprived, WIMD5=least deprived

Table C.10: Comparison of annual numbers of people receiving weak opioid prescriptions between 2005 and 2015 by deprivation area (Population adjusted data)

Year	Number of people per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	158.7	130.6	124.7	95.1	86.5
2006	159.9	132.3	126.7	97.0	87.9
2007	167.6	140.3	135.4	105.5	95.5
2008	172.4	144.9	140.8	110.8	99.5
2009	178.7	149.7	143.3	113.1	104.0
2010	180.4	152.8	145.5	115.4	105.0
2011	182.1	155.2	147.7	117.1	106.2
2012	183.2	156.0	147.3	117.5	106.4
2013	180.4	152.8	145.5	115.4	103.5
2014	178.0	150.0	144.5	113.3	102.7
2015	172.2	145.3	140.4	110.0	99.3
Change rate (%) 2005 - 2015	12.2	15.6	18.1	21.7	19.2

*Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most socio-economically deprived, WIMD5 = least socio-economically deprived

In the least deprived areas, the proportion of people receiving weak opioids increased 2.4% (from 14.5% to 14.9%) whereas the proportion of people receiving strong opioids in those areas reduced by 5.5% (from 14.3% to 13.5%).

Over the 11 years of the study period, the number of people living in the most deprived areas and receiving weak opioid prescriptions, increased 8.5% (from

158.7 to 172.2 people per 1000). Those in the least deprived areas, receiving weak opioid prescriptions increased by 14.7% (from 86.5 to 99.3 people per 1000 population) over that period. Whilst there were overall increases in the numbers of people receiving weak opioid prescriptions each year; the annual number of people in every area of Wales peaked in 2012 and subsequently reduced each year (Figure C.3).

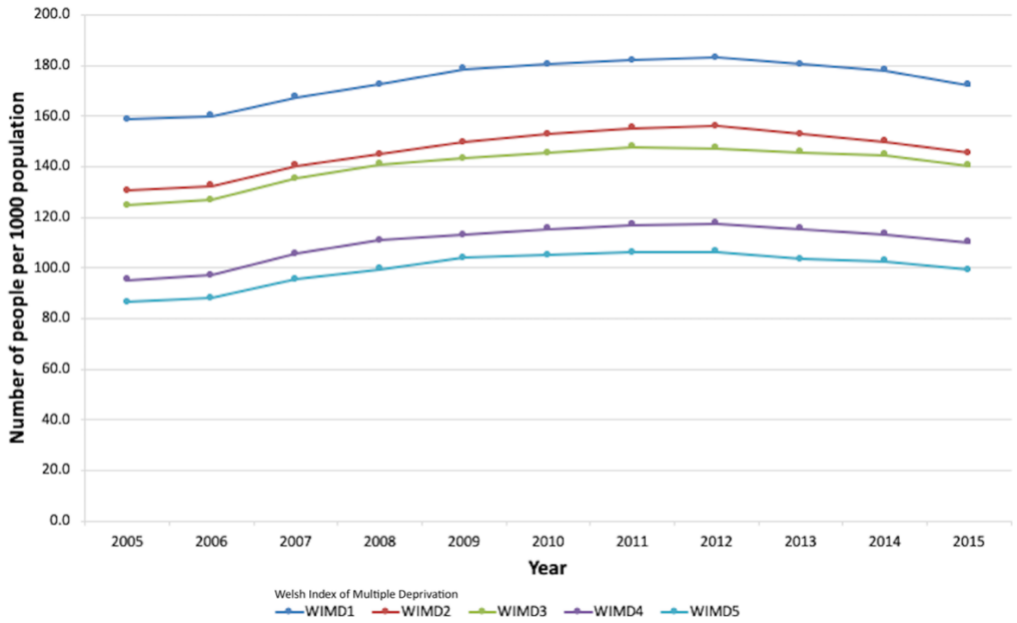


Figure C.3: Trends in the annual number of people receiving weak opioid prescriptions presented by deprivation area and adjusted to population of each area of deprivation in Wales
(WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 =least deprived

There were statistically significant differences between each deprivation area for the number of people receiving weak opioid prescriptions, ($p<.001$). However, post-hoc Dunn's pairwise and Bonferroni testing demonstrated significant differences between half of the compared pairs of deprivation areas (Table C.11).

Table C.11: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number people per 1000 receiving weak opioid prescriptions in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	.391			
3	.056	>.999		
4	<.001*	.025*	.206	
5	<.001*	<.001*	.006*	>.999

**p <0.05 = statistically significant. WIMD1=most socio-economically deprived, WIMD5=least socio-economically deprived*

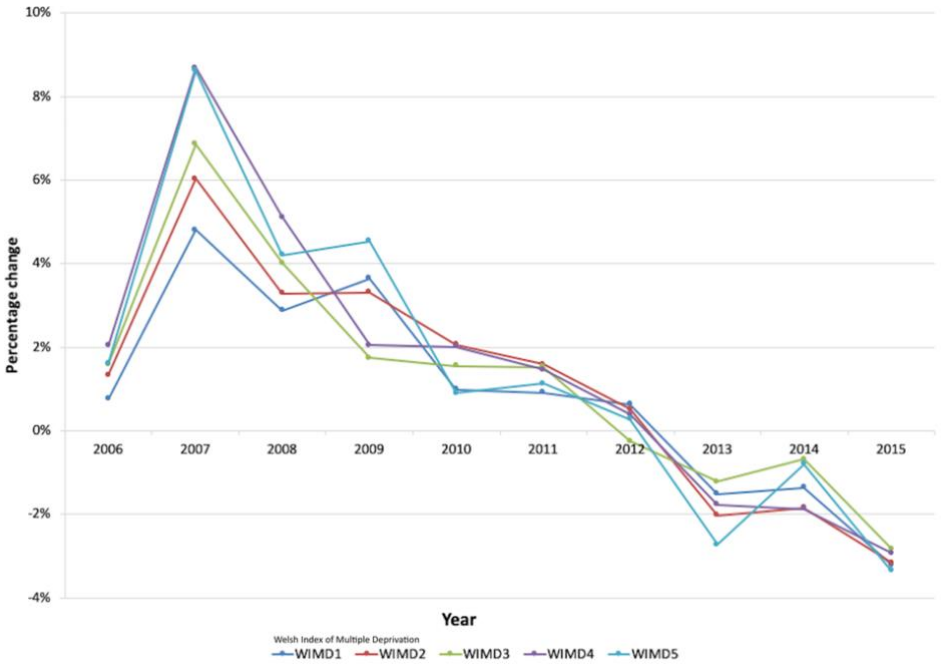


Figure C.4: Annual percentage change in the number of people prescribed weak opioids by area of deprivation in Wales
(WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived)

Table C.12: Comparison of annual numbers of people receiving strong opioid prescriptions between 2005 and 2015 by deprivation area (Population adjusted data)

Year	Number of people per 1000 population				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	5.3	4.7	4.9	3.7	3.1
2006	5.7	5.1	5.3	4.3	3.5
2007	6.4	5.9	5.8	4.8	3.9
2008	7.2	6.1	6.4	5.2	4.3
2009	8.1	6.8	7.1	5.8	4.7
2010	8.7	7.5	7.7	6.3	4.8
2011	9.8	8.3	8.4	6.8	5.5
2012	11.1	9.5	9.6	7.8	6.3
2013	12.7	10.7	11.0	8.6	7.0
2014	14.6	12.5	12.7	10.0	7.9
2015	16.5	14.0	14.3	10.9	8.7
Change rate (%) 2005 - 2015	211.6	200.0	192.5	191.5	180.5

*Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most socio-economically deprived, WIMD5 = least socio-economically deprived

The number of people receiving strong opioids increased in all areas between 2005 and 2015. Conversely to the weak opioid trends however, the greatest increase in the number of people receiving strong opioids was in the areas of highest deprivation (211.6%, from 5.3 to 16.5 people per 1000 population) and the areas of least deprivation saw a significant albeit smaller increase (180.5%, from 3.1 to 8.7 people per 1000 population) (Figure C.5).

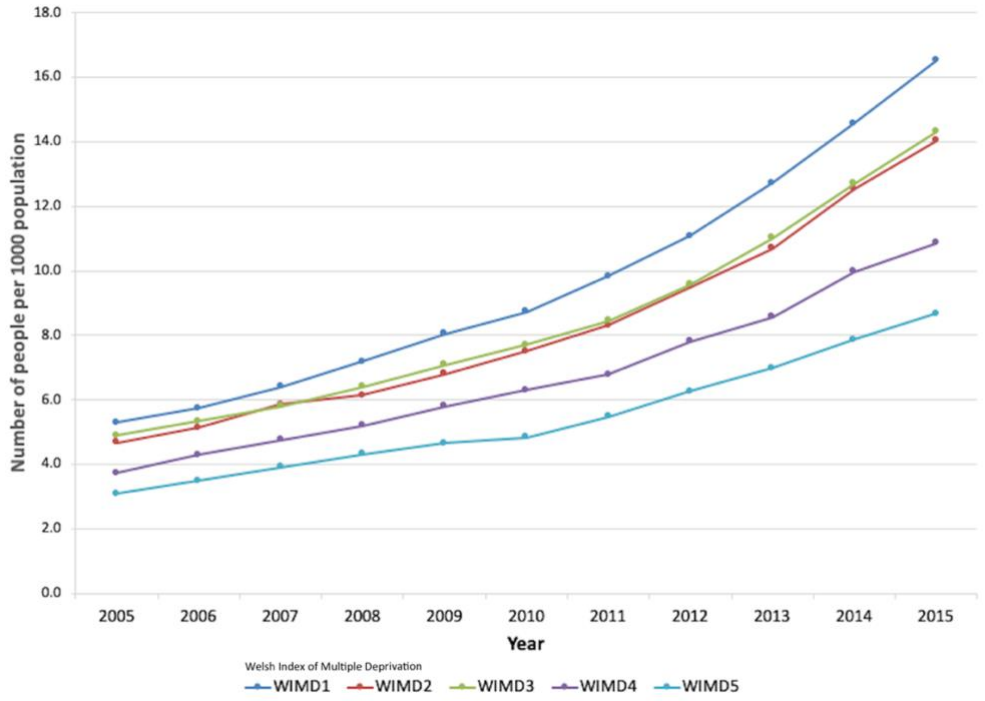


Figure C.5: Trends in the annual number of people receiving strong opioid prescriptions presented by deprivation area and adjusted to population of each area of deprivation in Wales
(WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5)

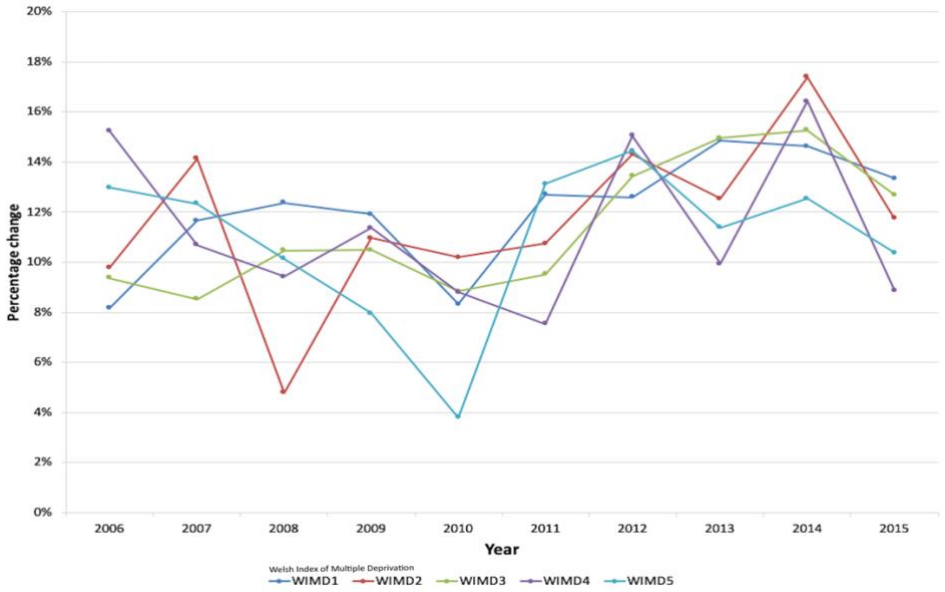


Figure C.6: Annual percentage change in the number of people prescribed strong opioids by each area of deprivation in Wales
(WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived)

A Kruskal-Wallis test to examine whether there was any difference between the number of people receiving in each of the WIMD areas receiving strong opioid prescriptions was statistically significant to 95% (p=.012). Post-hoc Dunn's pairwise and Bonferroni tests however, revealed that statistically significant difference (p=.013) only existed between the most deprived (WIMD1) (median=8.72) and least deprived (WIMD5) (median=4.84) areas in Wales (Table C.13).

Table C.13: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number people per 1000 receiving strong opioid prescriptions in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	.437	>.999	>.999	
5	<.013*	.224	.117	>.999

*p <0.05 = statistically significant. WIMD1=most deprived, WIMD5=least deprived

C.2.3 Number of prescriptions per 1000 quintile-population

Table C.14: Comparison of numbers of prescriptions for all opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015

	Prescriptions				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	468,209	365,651	315,481	213,808	191,128
2006	479,395	377,245	326,237	220,888	197,495
2007	511,937	404,814	348,966	242,883	214,680
2008	546,873	428,625	369,954	263,033	232,032
2009	573,347	450,463	389,448	279,393	244,183
2010	599,109	477,062	410,357	295,375	256,554
2011	629,842	505,328	435,569	311,598	270,458
2012	655,685	526,799	453,808	323,142	280,578
2013	669,980	531,688	461,424	328,837	286,035
2014	677,949	538,450	471,503	336,231	288,436
2015	681,386	541,863	473,611	336,065	290,619
Percentage change (%)	45.5	48.2	50.1	57.2	52.1

WIMD1 = most socio=economically deprived, WIMD5 = least socio-economically deprived

Table C.15: Comparison of quintile-population adjusted numbers of prescriptions for all opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015

	Prescriptions per 1000 population				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	987.1	774.8	702.4	487.0	399.7
2006	1005.1	795.0	722.3	500.4	410.7
2007	1066.0	847.3	767.4	546.4	443.4
2008	1131.4	891.3	808.3	587.9	476.1
2009	1196.1	935.9	841.4	615.3	503.9
2010	1244.6	987.8	883.6	648.4	526.9
2011	1302.3	1042.0	933.8	680.9	552.4
2012	1350.9	1082.7	969.7	703.9	570.9
2013	1376.0	1090.0	983.6	714.6	579.9
2014	1387.3	1100.4	1002.4	728.5	582.5
2015	1389.8	1104.8	1005.2	727.0	585.1
Change rate (%) 2005 - 2015	40.8	42.6	43.1	49.3	46.4

*Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most socio-economically deprived, WIMD5 = least socio-economically deprived

Table C.16: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of opioid prescriptions per 1000 population in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	.091	>.999		
4	<.001*	.016*	.291	

5	<.001*	<.001*	.008*	>.999

*p <0.05 = statistically significant WIMD1=most deprived, WIMD5=least deprived

Table C.17: Comparison of numbers of prescriptions for weak opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015

	Prescriptions				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	444,471	344,748	296,048	199,945	180,355
2006	450,544	353,396	302,192	204,078	183,923
2007	477,884	376,692	321,873	222,569	198,465
2008	506,624	396,352	339,457	238,008	212,901
2009	527,574	413,939	354,211	250,354	223,225
2010	546,577	434,307	369,303	261,486	232,104
2011	567,653	455,245	386,452	273,258	242,180
2012	582,792	468,921	395,403	280,183	248,146
2013	585,591	465,853	394,873	281,625	248,513
2014	583,292	462,801	398,911	284,188	247,871
2015	571,761	455,600	393,310	279,830	246,765
Percentage change (%) 2005-2015	28.6	32.2	32.9	40.0	36.8

WIMD1 = most socio=economically deprived, WIMD5 = least socio-economically deprived

Table C.18: Comparison of quintile-population adjusted numbers of prescriptions for weak opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015

	Number of prescriptions per 1000 population				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	937.1	730.5	659.1	455.4	377.2
2006	944.7	744.7	669.1	462.3	382.5
2007	995.1	788.4	707.8	500.7	409.9
2008	1048.1	824.2	741.6	532.0	436.9
2009	1100.6	860.0	765.3	551.4	460.6
2010	1135.5	899.3	795.2	574.0	476.7
2011	1173.7	938.8	828.5	597.2	494.7
2012	1200.7	963.7	844.9	610.3	504.9
2013	1202.7	955.0	841.7	612.0	503.8
2014	1193.6	945.8	848.0	615.8	500.6
2015	1166.2	928.9	834.8	605.3	496.8
Percentage change (%) 2005 - 2015	24.5	27.2	26.6	32.9	31.7

WIMD1 = most socio=economically deprived, WIMD5 = least socio-economically deprived

Table C.19: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of weak opioid prescriptions per 1000 population in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	.767			
3	.054	>.999		
4	<.001*	.015*	.311	
5	<.001*	<.001*	.008*	>.999

*p <0.05 = statistically significant WIMD1=most deprived, WIMD5-least deprived

Table C.20: Comparison of numbers of prescriptions for strong opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015

	Prescriptions				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5

2005	23,738	20,903	19,433	13,863	10,773
2006	28,851	23,849	24,045	16,810	13,572
2007	34,053	28,122	27,093	20,314	16,215
2008	40,249	32,273	30,497	25,025	19,131
2009	45,773	36,524	35,237	29,039	20,958
2010	52,532	42,755	41,054	33,889	24,450
2011	62,189	50,083	49,117	38,340	28,278
2012	72,893	57,878	58,405	42,959	32,432
2013	84,389	65,835	66,551	47,212	37,522
2014	94,657	75,649	72,592	52,043	40,565
2015	109,625	86,263	80,301	56,235	43,854
Percentage change (%) 2005-2015	361.8	312.7	313.2	305.6	307.1

WIMD1 = most socio=economically deprived, WIMD5 = least socio-economically deprived

Table C.21: Comparison of quintile-population adjusted numbers of prescriptions for strong opioid medicines by Welsh Index of Multiple Deprivation quintiles across Wales between 2005 and 2015

	Prescriptions per 1000 population				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	50.0	44.3	43.3	31.6	22.5
2006	60.5	50.3	53.2	38.1	28.2
2007	70.9	58.9	59.6	45.7	33.5
2008	83.3	67.1	66.6	55.9	39.3
2009	95.5	75.9	76.1	64.0	43.2
2010	109.1	88.5	88.4	74.4	50.2
2011	128.6	103.3	105.3	83.8	57.8
2012	150.2	119.0	124.8	93.6	66.0
2013	173.3	135.0	141.9	102.6	76.1
2014	193.7	154.6	154.3	112.8	81.9
2015	223.6	175.9	170.4	121.6	88.3
Change rate (%) 2005 - 2015	346.8	297.1	293.9	285.2	291.9

WIMD1 = most socioeconomically deprived, WIMD5 = least socio-economically deprived

Table C.22: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of strong opioid prescriptions per 1000 population in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	.474	>.999	>.999	
5	.006*	.100	.095	>.999

*p <0.05 = statistically significant.WIMD1=most deprived, WIMD5 = least deprived

C.2.4 Gender differences in the number of people receiving prescriptions by deprivation

C.2.4.1 All Opioids

Table C.23: Comparison of annual numbers of people by gender receiving strong opioid prescriptions between 2005 and 2015 by deprivation area (Population adjusted data)

Year	Men					Women				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	64.6	52.5	49.1	37.6	33.3	99.4	82.8	80.5	61.3	56.3
2006	65.5	53.6	51.2	38.8	34.2	100.1	83.8	80.9	62.5	57.1
2007	69.0	57.9	55.2	43	38	105	88.2	85.9	67.1	61.5
2008	72.0	59.7	58.1	45.4	40	107.6	91.3	89.1	70.7	63.9
2009	75.8	62.6	60.3	47	41.9	110.9	94	90.1	71.9	66.8
2010	76.8	64.7	61.3	48.6	43.2	112.3	95.6	91.9	73.1	66.6
2011	77.9	66.2	62.5	49.5	43.8	114	97.3	93.7	74.3	67.8
2012	79.6	67.1	62.9	50.2	44.3	114.7	98.3	94	75.1	68.4
2013	79.1	66.3	62.5	49.6	43.3	114	97.1	94.1	74.5	67.3
2014	78.3	65.9	63.2	49.4	43.3	114.2	96.6	94	73.9	67.3
2015	76.8	64.5	61.8	48.2	42.9	112	94.7	92.9	72.6	65.1
Change rate (%) 2005-2015	18.9	22.9	25.9	28.2	28.8	12.7	14.4	15.4	18.4	15.6

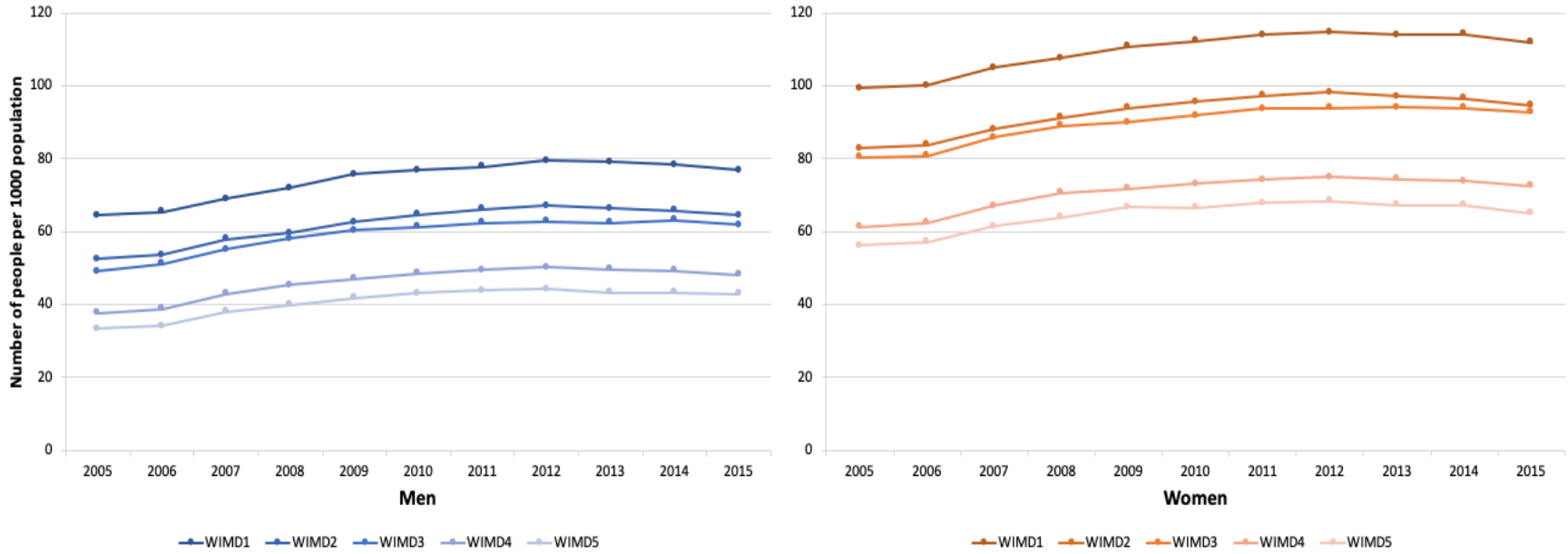


Figure C.7: Trends in the number of people receiving opioid prescriptions, stratified by gender and socioeconomic deprivation quintile
WIMD - Welsh Index of Multiple Deprivation, WIMD1=most deprived, WIMD5=least deprived

C.2.4.2 Weak opioids

Table C.24: Annual number of people per 1000 population receiving weak opioid prescriptions per deprivation quintile and gender

Year	Number of prescriptions per 1000 population									
	Men					Women				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5

2005	62.2	50.6	47.1	36.1	32.1	96.5	80	77.6	59.1	54.4
2006	63.1	51.5	49	37.1	33	96.8	80.8	77.7	59.9	54.9
2007	66.4	55.6	52.9	41.2	36.6	101.2	84.7	82.4	64.2	59
2008	69.1	57.3	55.7	43.5	38.5	103.3	87.6	85.1	67.4	61.1
2009	72.7	60	57.6	44.8	40.3	106	89.8	85.7	68.3	63.8
2010	73.4	61.8	58.4	46.2	41.5	107	91	87.1	69.2	63.5
2011	74.1	63	59.3	47	41.9	108	92.2	88.4	70.1	64.3
2012	75.2	63.5	59.3	47.3	42.1	108	92.5	88	70.2	64.3
2013	74	62.3	58.4	46.4	40.8	106.4	90.5	87.2	69.1	62.8
2014	72.6	61.2	58.4	45.6	40.5	105.3	88.8	86.1	67.7	62.2
2015	70.4	59.3	56.5	44.2	39.8	101.9	85.9	83.9	65.8	59.5
Change rate (%) 2005-2015	13.2	17.2	20.0	22.4	24.0	5.6	7.4	8.1	11.3	9.4

WIMD - Welsh Index of Multiple Deprivation, WIMD1=most deprived, WIMD5=least deprived

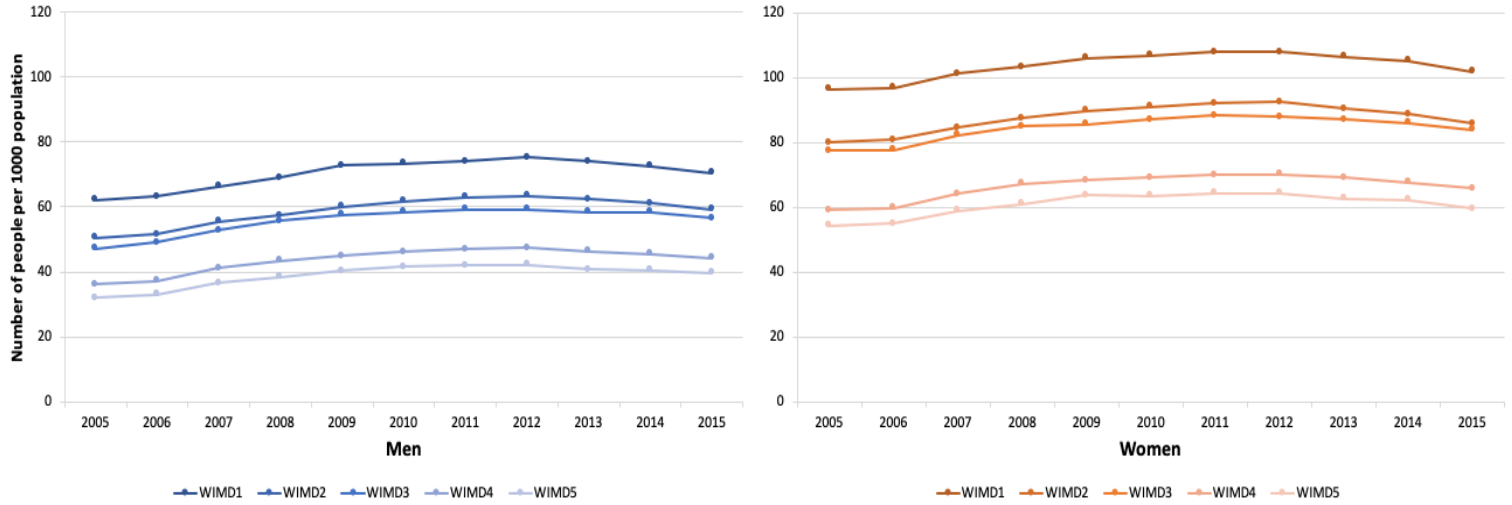


Figure C.8: Trends in the number of people per 1000 population receiving strong opioid by gender and socioeconomic deprivation quintile (WIMD)
(WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived)

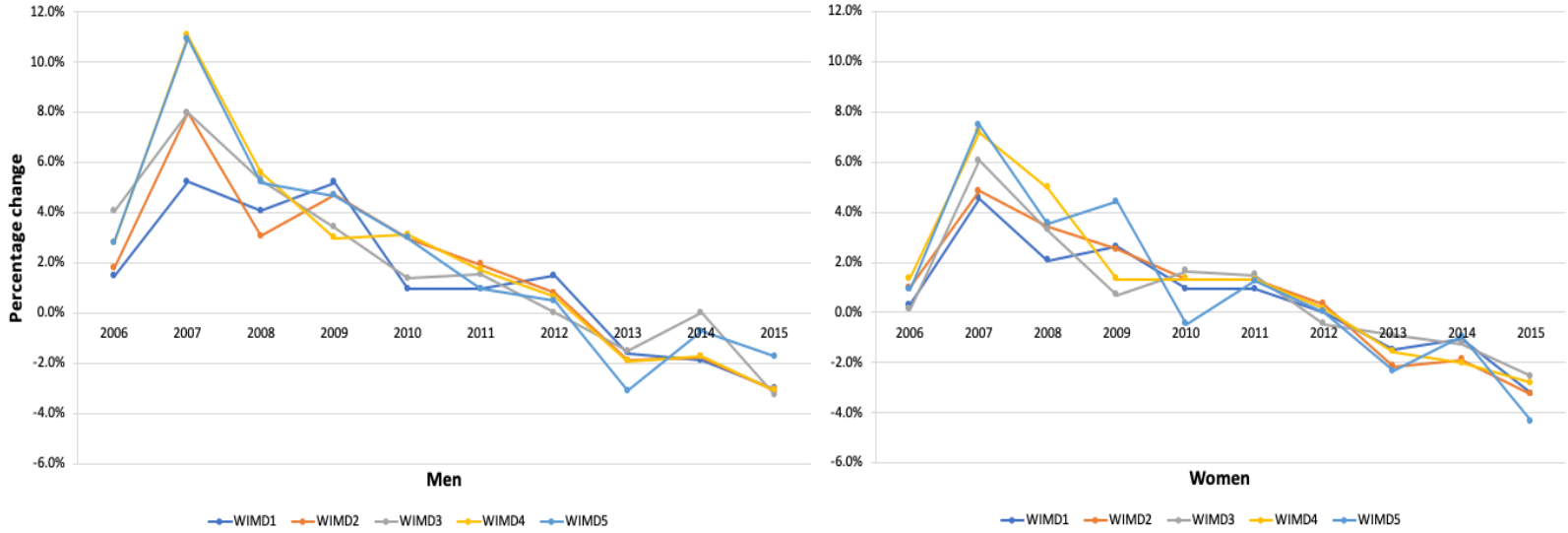


Figure C.9: Annual percentage change in the number of prescriptions weak opioids by gender and socioeconomic deprivation quintile (WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived)

C.2.4.3 Strong opioids

Table C.25: Annual number of people per 1000 population receiving strong opioid prescriptions per deprivation quintile and gender

Year	Men					Women				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	2.4	1.9	2	1.5	1.2	2.9	2.8	2.9	2.2	1.9
2006	2.4	2.1	2.2	1.7	1.2	3.3	3	3.2	2.6	2.2
2007	2.6	2.3	2.3	1.8	1.4	3.8	3.5	3.5	2.9	2.5
2008	2.9	2.4	2.4	1.9	1.5	4.3	3.7	4	3.3	2.8
2009	3.1	2.6	2.7	2.2	1.6	4.9	4.2	4.4	3.6	3
2010	3.4	2.9	2.9	2.4	1.7	5.3	4.6	4.8	3.9	3.1
2011	3.8	3.2	3.2	2.5	1.9	6	5.1	5.3	4.2	3.5
2012	4.4	3.6	3.6	2.9	2.2	6.7	5.8	6	4.9	4.1
2013	5.1	4	4.1	3.2	2.5	7.6	6.6	6.9	5.4	4.5
2014	5.7	4.7	4.8	3.8	2.8	8.9	7.8	7.9	6.2	5.1
2015	6.4	5.2	5.3	4	3.1	10.1	8.8	9	6.8	5.6
Change rate (%) 2005-2015	166.7	173.7	165.0	166.7	158.3	248.3	214.3	210.3	209.1	194.7

WIMD - Welsh Index of Multiple Deprivation, WIMD1=most deprived, WIMD5=least deprived

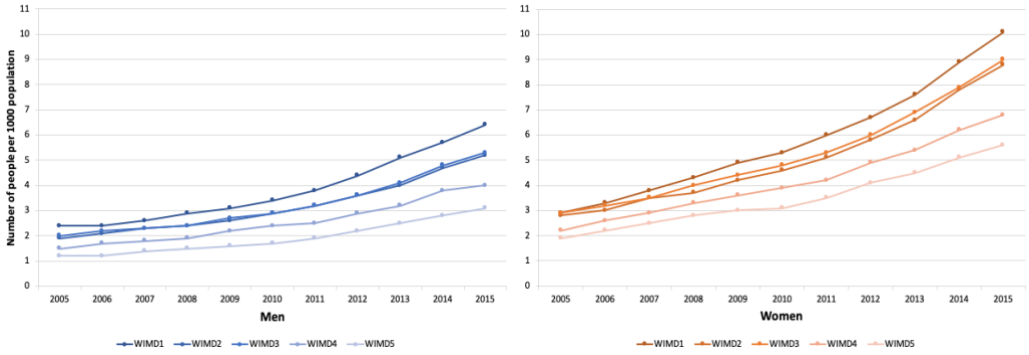


Figure C.10: Trends in the number of people per 1000 population receiving strong opioid by gender and socioeconomic deprivation quintile (WIMD)

WIMD = Welsh Index of Multiple Deprivation, WIMD1=most deprived, WIMD5=least deprived

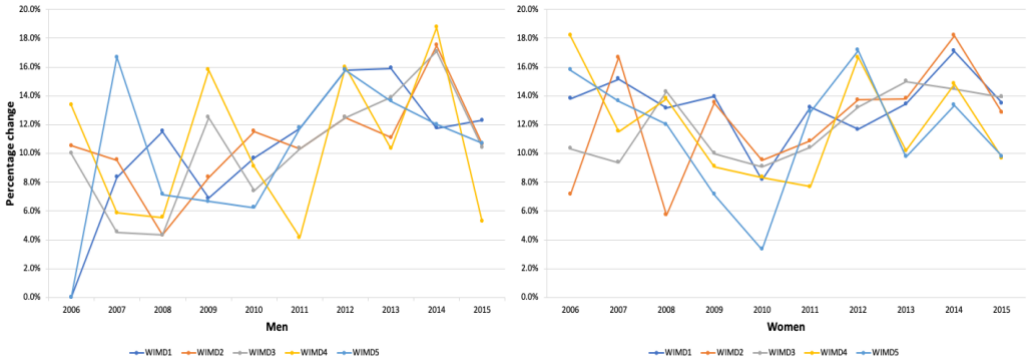


Figure C.11: Annual percentage change in the number of people receiving strong opioid prescriptions by gender and socioeconomic deprivation quintile

(WIMD = Welsh Index of Multiple Deprivation where WIMD1 = most deprived and WIMD5 = least deprived)

C.2.5 Gender differences in the number of prescriptions by deprivation

Table C.26: Comparison of numbers of prescriptions for all opioid medicines by Welsh Index of Multiple Deprivation quintiles and gender across Wales between 2005 and 2015

	Number of prescriptions per 1000 population									
	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2005	180,485	287,724	137,739	227,912	115,711	199,770	77,661	136,147	66,543	124,585
2006	186,937	292,458	143,091	234,154	120,974	205,263	80,922	139,966	69,375	128,120
2007	201,146	310,791	154,878	249,936	128,994	219,972	90,455	152,428	76,600	138,080
2008	215,423	331,450	164,964	263,661	137,332	232,622	98,359	164,674	83,167	148,865
2009	227,674	345,673	175,166	275,297	146,322	243,126	104,464	174,929	88,422	155,758
2010	239,540	359,569	187,131	289,931	155,761	254,596	111,290	184,085	92,972	163,582
2011	252,648	377,194	199,022	306,306	167,704	267,865	118,837	192,761	98,056	172,402
2012	265,923	389,762	207,338	319,461	176,429	277,379	123,102	200,040	102,365	178,213
2013	271,650	398,330	209,655	322,033	179,137	282,287	124,535	204,302	105,626	180,409
2014	273,306	404,643	211,997	326,453	183,512	287,991	128,256	207,975	106,618	181,818
2015	272,779	408,607	214,563	327,300	184,211	289,400	127,415	208,650	107,876	182,743
Change rate (%) 2005 - 2015	51.1	42.0	55.8	43.6	59.2	44.9	64.1	53.3	62.1	46.7

WIMD1 = most socioeconomically deprived, WIMD5 = least socioeconomically deprived

Table C.27: Comparison of quintile-population adjusted numbers of prescriptions for all opioid medicines by Welsh Index of Multiple Deprivation quintiles and gender across Wales between 2005 and 2015

	Number of prescriptions per 1000 population									
	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2005	380.5	606.6	290.4	480.5	244.0	421.2	163.7	287.0	140.3	262.7
2006	394.1	616.6	301.7	493.7	255.0	432.8	170.6	295.1	146.3	270.1
2007	424.1	655.2	326.5	526.9	272.0	463.8	190.7	321.4	161.5	291.1
2008	454.2	698.8	347.8	555.9	289.5	490.4	207.4	347.2	175.3	313.8
2009	480.0	728.8	369.3	580.4	308.5	512.6	220.2	368.8	186.4	328.4
2010	505.0	758.1	394.5	611.3	328.4	536.8	234.6	388.1	196.0	344.9
2011	532.7	795.2	419.6	645.8	353.6	564.7	250.5	406.4	206.7	363.5

2012	560.6	821.7	437.1	673.5	372.0	584.8	259.5	421.7	215.8	375.7
2013	572.7	839.8	442.0	678.9	377.7	595.1	262.6	430.7	222.7	380.4
2014	576.2	853.1	446.9	688.3	386.9	607.2	270.4	438.5	224.8	383.3
2015	575.1	861.5	452.4	690.0	388.4	610.1	268.6	439.9	227.4	385.3
Change rate (%)2005-2015	51.1	42.0	55.8	43.6	59.2	44.9	64.1	53.3	62.1	46.7
Mann-Whitney (between genders in same quintile)	p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187		p<.001*, η^2=0.717 d_{Cohen}=3.187	

*p<0.05 = statistically significant WIMD1 = most socioeconomically deprived, WIMD5 = least socio-economically deprived

Table C.28: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of all opioid prescriptions per 1000 population, issued to men in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	.084	>.999		
4	<.001*	.019*	.391	
5	<.001*	<.001*	.008*	>.999

*p <0.05 = statistically significant WIMD1=most deprived, WIMD5=least deprived

Table C.29: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of all opioid prescriptions per 1000 population, issued to women in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	.910			
3	.128	>.999		
4	<.001*	.017*	.192	
5	<.001*	<.001*	.005*	>.999

*p <0.05 = statistically significant. WIMD1=most deprived, WIMD5=least deprived

C.2.5.1 Weak opioids

Table C.30: Annual weak opioid prescriptions issued per socioeconomic deprivation quintile and gender

Year	**Men**					**Women**				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5

2005	169330	128356	107158	71727	62262	275141	216392	188890	128218	118093
2006	173510	132820	110733	74198	64477	277034	220576	191459	129880	119446
2007	185700	143001	117561	82139	70785	292184	233691	204312	140430	127680
2008	197585	151315	125221	87979	76615	309039	245037	214236	150029	136286
2009	208274	159860	132766	93001	81018	319300	254079	221445	157353	142207
2010	217625	169633	139628	97839	84848	328952	264674	229675	163647	147256
2011	227459	178409	147587	103679	88828	340194	276836	238865	169579	153352
2012	235539	183803	151927	106026	91338	347253	285118	243476	174157	156808
2013	237391	183623	151611	106719	91840	348200	282230	243262	174906	156673
2014	235446	181973	154159	108129	92517	347846	280828	244752	176059	155354
2015	229046	180077	151425	105933	93037	342715	275523	241885	173897	153728
Total	2316905	1792870	1489776	1037369	897565	3527858	2834984	2462257	1738155	1566883

WIMD - Welsh Index of Multiple Deprivation, WIMD1=most deprived, WIMD5=least deprived

Table C.31: Comparison of quintile-population adjusted numbers of prescriptions for weak opioid medicines by Welsh Index of Multiple Deprivation quintiles and gender across Wales between 2005 and 2015

	Number of prescriptions per 1000 population									
Year	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2005	357.0	580.1	270.6	456.2	225.9	398.2	151.2	270.3	131.3	249.0
2006	365.8	584.1	280.0	465.0	233.5	403.6	156.4	273.8	135.9	251.8
2007	391.5	616.0	301.5	492.7	247.9	430.7	173.2	296.1	149.2	269.2
2008	416.6	651.5	319.0	516.6	264.0	451.7	185.5	316.3	161.5	287.3
2009	439.1	673.2	337.0	535.7	279.9	466.9	196.1	331.7	170.8	299.8
2010	458.8	693.5	357.6	558.0	294.4	484.2	206.3	345.0	178.9	310.5
2011	479.5	717.2	376.1	583.6	311.2	503.6	218.6	357.5	187.3	323.3
2012	496.6	732.1	387.5	601.1	320.3	513.3	223.5	367.2	192.6	330.6
2013	500.5	734.1	387.1	595.0	319.6	512.9	225.0	368.7	193.6	330.3
2014	496.4	733.4	383.6	592.1	325.0	516.0	228.0	371.2	195.1	327.5
2015	482.9	722.5	379.7	580.9	319.2	510.0	223.3	366.6	196.1	324.1
Change rate (%) 2005 - 2015	35.3	24.6	40.3	27.3	41.3	28.1	47.7	35.6	49.4	30.2
Mann-Whitney (between genders in same quintile)	$p<.001^*$, $\eta^2=0.717$ $d_{Cohen}=3.187$		$p<.001^*$, $\eta^2=0.717$ $d_{Cohen}=3.187$		$p<.001^*$, $\eta^2=0.717$ $d_{Cohen}=3.187$		$p<.001^*$, $\eta^2=0.717$ $d_{Cohen}=3.187$		$p<.001^*$, $\eta^2=0.717$ $d_{Cohen}=3.187$	

*p<0.05 = statistically significant. WIMD1 = most socioeconomically deprived, WIMD5 = least socioeconomically deprived

Table C.32: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of weak opioid prescriptions per 1000 population, issued to men in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	.910			
3	.061	>.999		
4	<.001*	.012*	.291	
5	<.001*	<.001*	.008*	>.999

*p <0.05 = statistically significant. WIMD1=most deprived, WIMD5=least deprived

Table C.33: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of weak opioid prescriptions per 1000 population, issued to women in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	.553			
3	.046*	>.999		
4	<.001*	.020*	.301	
5	<.001*	<.001*	.007*	>.999

*p <0.05 = statistically significant. WIMD1=most deprived, WIMD5=least deprived

C.2.5.2 Strong opioids

Table C.34: Annual strong opioid prescriptions issued per deprivation quintile and gender

Year	Men					Women				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	11,155	9,383	8,553	5,934	4,281	12,583	11,520	10,880	7,929	6,492
2006	13,427	10,271	10,241	6,724	4,898	15,424	13,578	13,804	10,086	8,674
2007	15,446	11,877	11,433	8,316	5,815	18,607	16,245	15,660	11,998	10,400
2008	17,838	13,649	12,111	10,380	6,552	22,411	18,624	18,386	14,645	12,579
2009	19,400	15,306	13,556	11,463	7,404	26,373	21,218	21,681	17,576	13,551
2010	21,915	17,498	16,133	13,451	8,124	30,617	25,257	24,921	20,438	16,326
2011	25,189	20,613	20,117	15,158	9,228	37,000	29,470	29,000	23,182	19,050

2012	30,384	23,535	24,502	17,076	11,027	42,509	34,343	33,903	25,883	21,405
2013	34,259	26,032	27,526	17,816	13,786	50,130	39,803	39,025	29,396	23,736
2014	37,860	30,024	29,353	20,127	14,101	56,797	45,625	43,239	31,916	26,464
2015	43,733	34,486	32,786	21,482	14,839	65,892	51,777	47,515	34,753	29,015
Total	270,606	212,674	206,311	147,927	100,055	378,343	307,460	298,014	227,802	187,692

WIMD - Welsh Index of Multiple Deprivation, WIMD1=most deprived, WIMD5=least deprived

Table C.35: Comparison of quintile-population adjusted numbers of prescriptions for strong opioid medicines by Welsh Index of Multiple Deprivation quintiles and gender across Wales between 2005 and 2015

	Number of prescriptions per 1000 population									
	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2005	23.5	26.5	19.8	24.3	18.0	22.9	12.5	16.7	9.0	13.7
2006	28.3	32.5	21.7	28.6	21.6	29.1	14.2	21.3	10.3	18.3
2007	32.6	39.2	25.0	34.2	24.1	33.0	17.5	25.3	12.3	21.9
2008	37.6	47.2	28.8	39.3	25.5	38.8	21.9	30.9	13.8	26.5
2009	40.9	55.6	32.3	44.7	28.6	45.7	24.2	37.1	15.6	28.6
2010	46.2	64.5	36.9	53.2	34.0	52.5	28.4	43.1	17.1	34.4
2011	53.1	78.0	43.5	62.1	42.4	61.1	32.0	48.9	19.5	40.2
2012	64.1	89.6	49.6	72.4	51.7	71.5	36.0	54.6	23.2	45.1
2013	72.2	105.7	54.9	83.9	58.0	82.3	37.6	62.0	29.1	50.0
2014	79.8	119.7	63.3	96.2	61.9	91.2	42.4	67.3	29.7	55.8
2015	92.2	138.9	72.7	109.2	69.1	100.2	45.3	73.3	31.3	61.2
Change rate (%) 2005 - 2015	292.0	423.7	267.5	349.5	283.3	336.7	262.0	338.3	246.6	346.9
Mann-Whitney (between genders in same quintile)	p=.193, η^2=0.082 d_{Cohen}=0.599		p=.116, η^2=0.118 d_{Cohen}=0.73		p=.101, η^2=0.127 d_{Cohen}=0.764		p=.056, η^2=0.165 d_{Cohen}=0.889		p<.01*, η^2=0.298 d_{Cohen}=1.303	

*p<0.05 = statistically significant. WIMD1 = most socioeconomically deprived, WIMD5 = least socioeconomically deprived

Table C.36: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of strong opioid prescriptions per 1000 population, issued to men in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	.229	>.999	>.999	
5	<.001*	.020*	.021*	.570

*p <0.05 = statistically significant. WIMD1=most deprived, WIMD5=least deprived

Table C.37: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of strong opioid prescriptions per 1000 population, issued to women in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	.885	>.999	>.999	
5	.048*	.391	.291	>.999

*p <0.05 = statistically significant. WIMD1=most deprived, WIMD5=least deprived

Appendix D Prescribing trends by drug, oral morphine equivalence

D.1 Number of people receiving prescriptions, stratified by drug

Table D.1: Trends in the number of people receiving prescriptions 2005 - 2015, stratified by drug

Year	Number of people receiving prescriptions							
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Total
2005	2421	187808	76482	2377	4552	1285	47452	354570
2006	3893	202378	73947	2993	4828	1461	52226	350641
2007	5303	222913	73904	3535	5557	1864	56792	374383
2008	6766	237076	71433	3889	6342	2380	59393	390504
2009	7824	245827	69187	3967	6981	3301	63746	403653
2010	8696	252226	65879	4202	8092	3679	67435	412776
2011	9262	258633	62507	4234	9919	3822	69840	420564
2012	9032	261372	58319	4304	12608	4090	72153	424301
2013	8643	257740	54940	4319	15756	3744	69703	417424
2014	8421	261062	50673	4254	19531	3711	62621	413451
2015	8485	260646	46827	4040	22818	3989	54325	404938
Percentage change (%) 2005-2015	250.5	38.8	-38.8	70.0	401.3	210.4	14.5	14.2

Table D.2: Trends in the number of people per 1000 population, receiving opioid analgesic prescriptions 2005 - 2015, stratified by drug

Year	Number of people per 1000 population							
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other
2005	1.0	81.1	33.0	1.0	2.0	0.6	20.5	13.9
2006	1.7	86.9	31.8	1.3	2.1	0.6	22.4	3.8
2007	2.3	95.1	31.5	1.5	2.4	0.8	24.2	1.9
2008	2.9	100.5	30.3	1.6	2.7	1.0	25.2	1.4
2009	3.3	104.0	29.3	1.7	3.0	1.4	27.0	1.2
2010	3.7	106.3	27.8	1.8	3.4	1.5	28.4	1.1
2011	3.9	108.4	26.2	1.8	4.2	1.6	29.3	1.0
2012	3.8	109.2	24.4	1.8	5.3	1.7	30.1	1.0
2013	3.6	107.4	22.9	1.8	6.6	1.6	29.0	1.1

2014	3.5	108.4	21.0	1.8	8.1	1.5	26.0	1.3
2015	3.5	108.0	19.4	1.7	9.5	1.7	22.5	1.6
Rate change (%)2005-2015	236.2	33.1	-41.3	63.0	380.9	197.8	9.8	-88.7

D.1.1 Annual number of prescriptions by drug

Table D.3: Trends in the number of prescriptions issued 2005 - 2015, stratified by drug

Year	**Number of prescriptions**								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
2005	19,059	812,403	364,488	14,462	39,175	12,623	220,149	131,058	1,613,417
2006	27,139	888,403	361,947	20,932	44,987	15,738	257,652	39,534	1,656,332
2007	36,905	973,514	362,142	27,539	53,259	19,734	287,450	22,557	1,783,100
2008	47,808	1,050,084	354,498	33,249	62,808	26,940	312,421	16,543	1,904,351
2009	58,591	1,100,773	341,850	37,522	70,967	36,036	341,727	15,085	2,002,551
2010	70,809	1,152,691	330,325	41,749	84,417	44,492	369,896	14,193	2,108,572
2011	79,097	1,207,202	322,668	44,561	106,043	53,938	400,437	13,091	2,227,037
2012	82,179	1,245,621	307,635	46,852	135,234	60,719	427,030	13137	2,318,407
2013	8,1934	1,252,940	293,774	48,274	173,286	60,602	434,130	13,766	2,358,706
2014	83,036	1,286,777	281,823	46,723	211,894	59,,524	414,720	14,221	2,398,718
2015	84,200	1,311,224	268,230	44,221	251,467	62,036	377,323	16,673	2,415,374
Percentage change (%) 2005 – 2015	341.8%	61.4%	-26.4%	205.8%	541.9%	391.5%	71.4%	-87.3%	49.7%

D.1.2 Annual number of prescriptions per 1000 population by drug

Table D.4: Trends in the number of opioid prescriptions per 1000 population 2005 – 2015, stratified by drug

Year	**Prescriptions per 1000 population**								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
2005	8.2	350.9	157.4	6.2	16.9	5.5	95.1	56.6	696.8
2006	11.7	381.6	155.5	9.0	19.3	6.8	110.7	17.0	711.4
2007	15.7	415.3	154.5	11.7	22.7	8.4	122.6	9.6	760.6
2008	20.3	445.0	150.2	14.1	26.6	11.4	132.4	7.0	807.1

2009	24.8	465.5	144.6	15.9	30.0	15.2	144.5	6.4	846.8
2010	29.8	485.6	139.2	17.6	35.6	18.7	155.8	6.0	888.2
2011	33.2	506.2	135.3	18.7	44.5	22.6	167.9	5.5	933.8
2012	34.3	520.5	128.5	19.6	56.5	25.4	178.4	5.5	968.7
2013	34.1	522.1	122.4	20.1	72.2	25.3	180.9	5.7	982.8
2014	34.5	534.4	117.0	19.4	88.0	24.7	172.2	5.9	996.2
2015	34.9	543.3	111.1	18.3	104.2	25.7	156.3	6.9	1000.7
Percentage change (%) 2005 – 2015	323.8	54.8	-29.4	193.3	515.8	371.5	64.4	-87.8	43.6

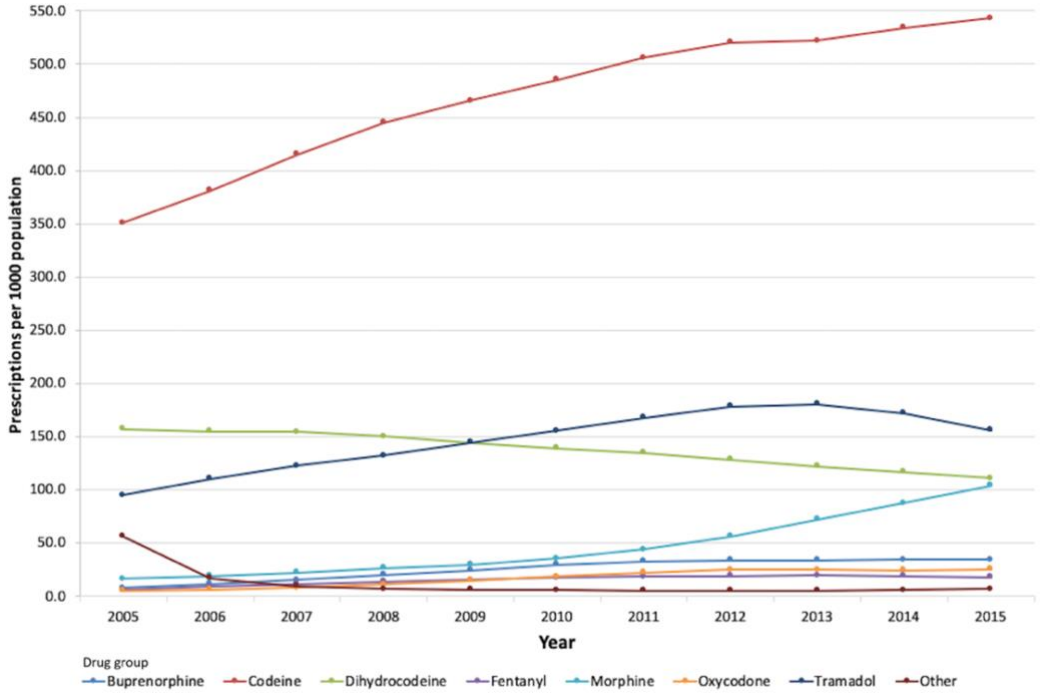


Figure D.1: Trends in number of prescriptions per 1000 population, stratified by drug between 2005 - 2015

Table D.5: Dunn's pairwise tests with Bonferroni corrections demonstrating relationship between the number of opioid prescriptions, examined by which drug was prescribed

Drug name	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	.001*						
Dihydrocodeine	.199	>.999					
Fentanyl	>.999	<.001*	.001*				
Morphine	>.999	.010*	.858	>.999			
Oxycodone	.657	<.001*	<.001*	>.999	.145		
Tramadol	.382	>.999	>.999	.003*	>.999	<.001*	
Other	>.999	<.001*	..001*	>.999	.781	>.999	.001*

*p<0.05 is significant

D.1.3 Analysis of prescribing rates for opioid analgesics classed as 'other'

Table D.6: Trends in the number of prescriptions issued for drugs classified as 'other', 2005-2015

Year	Number of prescriptions issues								
	Dextropropoxyphene	Diamorphine	Dipipanone	Hydromorphone	Meptazinol	Methadone	Pentazocine	Pethidine	Tapentadol
2005	120842	1004	1137	186	2289	528	640	4432	252
2006	28413	998	1331	197	2138	603	626	5228	1047
2007	12009	963	1206	210	1874	569	569	5157	2059
2008	6149	1162	1283	166	1793	594	392	5004	2724
2009	5048	1071	1203	192	1700	567	395	4909	4904
2010	4424	1083	1208	168	1574	452	437	4847	
2011	3228	1269	945	142	1391	558	438	4868	
2012	2632	1676	696	222	1286	532	393	4653	
2013	2296	2124	649	315	1202	473	337	4311	
2014	2204	3580	503	211	1105	550	287	3057	
2015	1963	4471	358	141	990	571	235	3040	
Percentage change (%) 2005 – 2015	-98.4	345.3	-68.5	-24.2	-56.7	8.1	-63.3	-31.4	1846.0

Table D.7: Trends in the annual number of prescriptions for 'other' opioids 2005 - 2015. Data adjusted to number per 1000 population

	Prescriptions per 1000 population receiving named opioid prescriptions

	Dextropropoxyphene	Diamorphine	Dipipanone	Hydromorphone	Meptazinol	Methadone	Pentazocine	Pethidine	Tapentadol
2005	52.189	0.434	0.491	0.080	0.989	0.228	0.276	1.914	0<.001
2006	12.204	0.429	0.572	0.085	0.918	0.259	0.269	2.245	0<.001
2007	5.123	0.411	0.514	0.090	0.799	0.243	0.243	2.200	0<.001
2008	2.606	0.492	0.544	0.070	0.760	0.252	0.166	2.121	0<.001
2009	2.135	0.453	0.509	0.081	0.719	0.240	0.167	2.076	0<.001
2010	1.864	0.456	0.509	0.071	0.663	0.190	0.184	2.042	0<.001
2011	1.354	0.532	0.396	0.060	0.583	0.234	0.184	2.041	0.106
2012	1.100	0.700	0.291	0.093	0.537	0.222	0.164	1.944	0.437
2013	0.957	0.885	0.270	0.131	0.501	0.197	0.140	1.796	0.858
2014	0.915	1.487	0.209	0.088	0.459	0.228	0.119	1.270	1.131
2015	0.813	1.852	0.148	0.058	0.410	0.237	0.097	1.260	2.032
Percentage change (%) 2005-2015	-98.4	327.2	-69.8	-27.3	-58.5	3.7	-64.8	-34.2	1822.8
Spearman's r, p value*	<-.999, p<.001*	0.968, p<.001*	-0.818, p<0.01*	0.064, p=0.853	<-.999, p<.001*	-0.227, p=0.502	-0.873, p<.001*	-0.733, p<0.05*	Not calculated

*p-value <0.05 = statistically significant

Table D.8: Dunn's pairwise tests with Bonferroni corrections demonstrating relationship between the number of opioid prescriptions, examined by which drug was prescribed

Drug name	**Dextropropoxyphene**	**Diamorphine**	**Dipipanone**	**Hydromorphone**	**Meptazinol**	**Methadone**	**Pentazocine**	**Pethidine**
Diamorphine	>.999							
Dipipanone	.086	>.999						
Hydromorphone	<.001*	.003*	.106					
Meptazinol	>.999	>.999	>.999	.001*				
Methadone	.001*	>.999	>.999	>.999	.587			
Pentazocine	<.001*	.256	>.999	>.999	.118	>.999		
Pethidine	>.999	.924	.050*	<.001*	>.999	<.001*	<.001*	
Tapentadol	<.001*	.442	>.999	>.999	.202	>.999	>.999	<.001*

*p<0.05 is significant

There was a significant difference (Kruskal-Wallis p<.001, η^2= 0.778. d_{Cohen}= 3.75) in the number of prescriptions issued of the different opioids classified as 'other' in this study as determined by a Kruskal-Wallis test. Post-hoc Dunn's pairwise tests, and Bonferroni adjustments demonstrated significantly fewer prescriptions for hydromorphone compared to dextropropoxyphene, diamorphine, meptazinol and pethidine (Table D.8). Other differences were noted in pairwise comparison although given the lower prescribing rates for all these medicines, the clinical significance of these findings is likely to be limited. Six of the nine medicines included in the 'other' group of opioid analgesics were observed to have reductions in prescribing between 2005 and 2015, confirmed by negative Spearman's r results (Table D.7).

Dextropropoxyphene had a 98.4% (from 52.2 to 0.8 prescriptions per 1000 population) reduction in the number of annual prescriptions issued between 2005 and 2015. In 2005, the dextropropoxyphene prescriptions was more than 650 times greater than the least prescribed opioid, hydromorphone (Figure D.2). In 2015, tapentadol was the most frequently prescribed 'other' opioid – accounting for 2 prescriptions per 1000 people, which equated to 0.2% of the total of all opioid prescriptions examined in the study (Figure D.2).

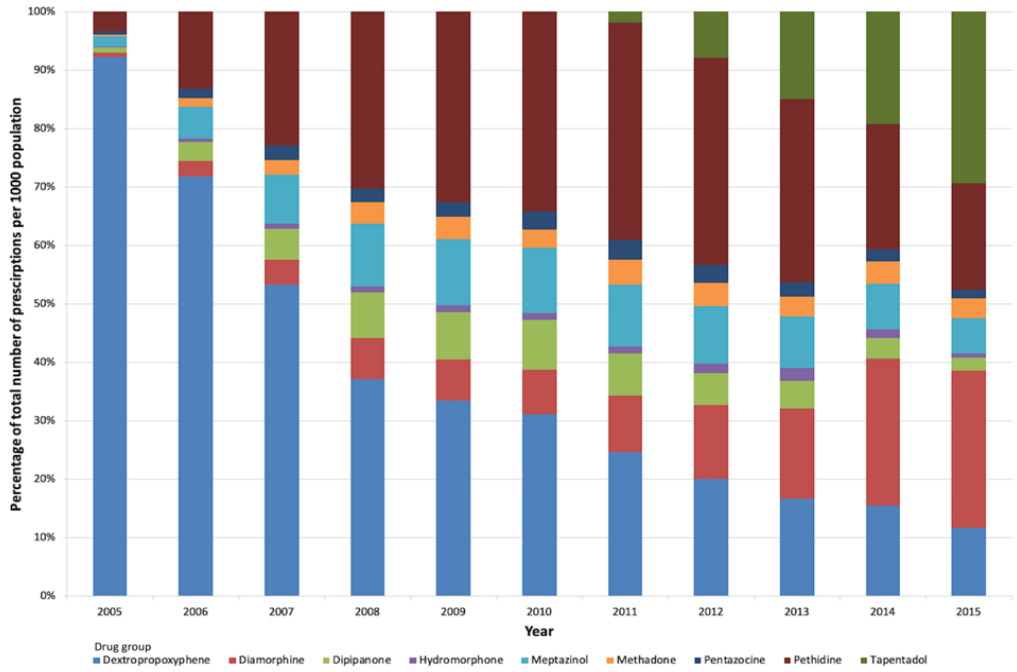


Figure D.2: Trend in the number of prescriptions of named opioids by percentage of the total number of people issued opioid prescriptions categorised as 'other' in the study protocol

D.2 Oral morphine equivalence

Table D.9: Daily oral morphine equivalent dose (milligrams) issued on prescription, given as annual totals, and stratified by drug

Year	Oral morphine equivalent dose (milligrams) prescribed								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
2005	977,677	13,418,363	4,620,630	2,704,640	3,284,610	1,343,350	7,861,525	3,456,828	37,667,623
2006	1,297,958	14,812,688	4,565,578	3,748,545	3,755,130	1,633,260	9,310,730	1,077,115	40,201,004
2007	1,528,732	16,472,069	4,584,342	4,676,595	4,513,110	1,960,460	10,546,155	620,756	44,902,219
2008	1,717,634	18,008,755	4,510,564	5,437,230	5,242,780	2,636,820	11,615,165	448,050	49,616,998
2009	2,027,878	19,279,480	4,357,848	6,045,195	5,785,330	3,456,140	12,800,175	410,189	54,162,235
2010	2,339,484	20,508,656	4,221,454	6,677,120	6,667,420	4,224,140	13,938,800	393,050	58,970,124
2011	2,596,580	21,828,568	4,142,234	6,965,715	8,113,590	5,279,440	15,193,800	375,278	64,495,205
2012	2,671,866	22,931,778	3,974,680	7,124,570	10,083,060	6,164,520	16,280,490	425,250	69,656,214
2013	2,634,718	23,371,640	3,816,478	7,289,820	12,331,790	6,236,820	16,561,625	491,838	72,734,729
2014	2,683,534	24,327,146	3,723,046	6,982,015	14,775,830	6,047,200	15,789,745	508,316	74,836,832
2015	2,672,408	25,220,520	3,591,820	6,496,270	17,091,470	6,165,400	14,253,325	702,447	76,193,660
Percentage change (%) 2005 – 2015	182.0	86.2	-20.5	141.0	417.7	368.3	81.2	-79.7	102.9

Table D.10: Daily oral morphine equivalent dose (milligrams) issued on prescription, adjusted to 1000population, stratified by drug

Year	Estimated oral morphine equivalent dose (milligrams) per 1000 population								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
2005	422	5,795	1,996	1,168	1,419	580	3,395	1,493	16,268
2006	557	6,362	1,961	1,610	1,613	701	3,999	463	17,267
2007	652	7,026	1,956	1,995	1,925	836	4,499	265	19,154
2008	728	7,632	1,912	2,304	2,222	1,117	4,923	190	21,028
2009	858	8,153	1,843	2,556	2,446	1,462	5,413	173	22,904
2010	986	8,639	1,778	2,813	2,809	1,779	5,872	166	24,841
2011	1,089	9,153	1,737	2,921	3,402	2,214	6,371	157	27,043
2012	1,116	9,582	1,661	2,977	4,213	2,576	6,803	178	29,106
2013	1,098	9,738	1,590	3,037	5,138	2,599	6,901	205	30,307
2014	1,115	10,104	1,546	2,900	6,137	2,512	6,558	211	31,081
2015	1,107	10,449	1,488	2,691	7,081	2,554	5,905	291	31,568

Rate change (%) 2005 – 2015	162.2	80.3	-25.4	130.4	399.2	340.3	73.9	-80.5	94.1

*p<0.05 is statistically significant

D.2.1 $OMEQ_e$ per prescription

When each drug was stratified by $OMEQ_e$ per prescription issued, there was an overall increase of 35.5% (from 23 milligrams to 32 milligrams $OMEQ_e$ per prescription) between 2005 and 2015 (Table D.11). The four drugs classified as 'strong' opioids for this study, all demonstrated reductions in $OMEQ_e$ per prescription issued over the period examined (Figure D.3). Buprenorphine $OMEQ_e$ reduced by 61.7% and this appeared to be due to a reduction in high-dose transdermal delivery systems (TDS) (patches) and oral preparations (preparations not being used for the treatment of drug misuse). However, the number of prescriptions issued for buprenorphine hugely increased due to the use of low-dose TDS (Table D.3).

Table D.11: Oral morphine equivalent dose per prescription issued for stated drug and subsequent percentage change in OMEQe per prescription between 2005 and 2015, in addition to the number of prescriptions issued per 1000 population and percentage change over the study period

	Estimated oral morphine equivalent dose per prescription issued (milligrams)								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
2005	97.7	16.5	12.7	187.1	85.5	107.1	35.7	26.6	23.5
2006	75.2	16.7	12.6	179.1	84.4	104.4	36.1	28.2	24.4
2007	57.5	16.9	12.7	169.8	85.2	99.7	36.7	29.4	25.4
2008	45.7	17.1	12.7	163.5	83.9	98.2	37.2	29.9	26.2
2009	41.5	17.5	12.7	161.1	81.9	96.2	37.5	30.2	27.2
2010	39.3	17.8	12.8	159.9	79.6	95.1	37.7	30.8	28.1
2011	38.3	18.1	12.8	156.3	77.3	98.1	37.9	32.4	29.1
2012	37.5	18.4	12.9	152.1	75.0	101.7	38.1	37.8	30.2
2013	36.6	18.7	13.0	151.0	71.6	103.3	38.2	42.9	31.0
2014	36.6	18.9	13.2	149.4	70.1	102.1	38.1	48.6	31.4
2015	36.3	19.2	13.4	147.0	68.2	99.8	37.8	58.1	31.8
Percentage change (%) 2005-2015	-62.9	16.5	5.6	-21.4	-20.2	-6.8	5.8	118.0	35.1

Whilst the number of prescriptions for 'other' opioids reduced, primarily due to the removal of dextropropoxyphene containing medicines from the UK market, an increase in $OMEQ_e$ was seen towards the end of the study period (Figure D.3**).** This appears to be a consequence of tapentadol prescribing, a drug introduced in the UK in 2011 and which has a high morphine equivalent dose.

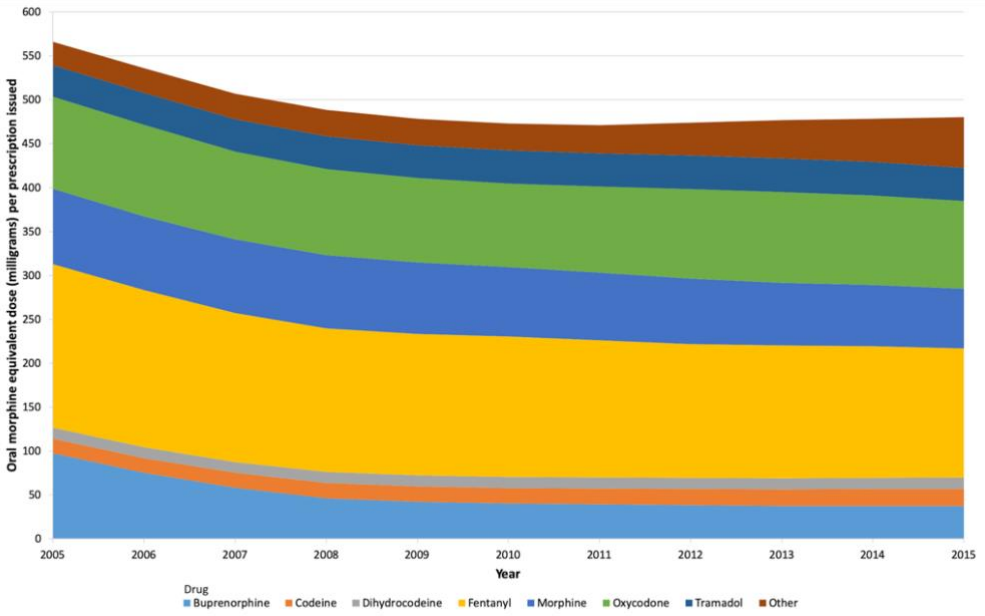


Figure D.3: Trends in the daily oral morphine equivalent dose per prescription issued for stated drug, between 2005 – 2015

Fentanyl had the highest daily $OMEQ_e$ per prescription of all opioids being issued (Table D.11) with oxycodone the next highest (Figure D.3). Whilst the number of morphine prescriptions increased by nearly six times over the 11 years, examined, the $OMEQ_e$ per prescription reduced over the same time by 20.6% (from 86 to 68 milligrams per prescription) (Table D.11). The differences in $OMEQ_e$ per prescription when stratified by the drug prescribed, were significantly different (Kruskal-Wallis $p<.001$, $\eta^2= 0.943$. $d_{Cohen}= 8.10$). Significantly lower $OMEQ_e$ per prescription were observed for codeine compared to the three most prescribed strong opioids, fentanyl, morphine, and oxycodone. This was also the case for dihydrocodeine, which also had lower $OMEQ_e$ than buprenorphine. Tramadol OMEQe per prescription was significantly lower than seen for fentanyl and oxycodone (.

Table D.12).

Table D.12: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the daily oral morphine equivalent doses per prescription, by drug

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	0.121						
Dihydrocodeine	0.003*	>.999					
Fentanyl	0.037*	<.001*	<.001*				
Morphine	>.999	.002*	<.001*	.899			
Oxycodone	0.827	<.001*	<.001*	>.999	>.999		
Tramadol	>.999	>.999	0.056	<.001*	0.928	0.034*	
Other	>.999	>.999	0.197	<.001*	0.517	0.015*	>.999

*p<0.05 is statistically significant

D.2.2 $OMEQ_e$ for products of greater than 120mg

Examining the trend in prescriptions for doses of opioids that were equivalent or more than 120mg morphine per day, (based on the strength of the preparation prescribed), demonstrated increases in all 4 strong opioids commonly prescribed (Table D.13). Whilst there were similar percentage increases in the $OMEQ_e$ for morphine (337.6%, from 1098 to 4805 milligrams per 1000 population) and oxycodone (321.5%, from 393to 1659 milligrams per 1000 population) (Table D.13), the total $OMEQ_e$ for high-dose morphine was nearly three times that of high-dose oxycodone throughout the study period (Figure D.5). There was a large percentage increase (485.6%, from 25 to 146 milligrams per 1000 population) in the $OMEQ_e$ of 'other' opioids from 2011 which was due to prescribing of tapentadol.

Table D.13: Trends in annual total oral morphine equivalent dose per 1000 population, stratified by drug and rate change for 2005 - 2015

Year	Annual total daily oral morphine equivalent dose (milligrams) per 1000 population				
	Buprenorphine	Fentanyl	Morphine	Oxycodone	Other
2005	205	952	1098	393	25
2006	276	1284	1236	468	24
2007	296	1559	1470	534	16
2008	264	1769	1683	703	14
2009	292	1949	1822	913	13
2010	321	2150	2068	1106	15
2011	337	2202	2450	1400	20
2012	337	2209	3009	1683	44
2013	330	2240	3580	1737	64
2014	345	2133	4214	1674	84
2015	339	1952	4805	1659	146
Rate change (%) 2005-2015	65.3	105.0	337.6	321.5	485.6

Table D.14: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the daily oral morphine equivalent doses per prescription for high-dose prescriptions (>120 milligrams OMEQe), by drug

Drug	Buprenorphine	Fentanyl	Morphine	Oxycodone
Fentanyl	.007*			
Morphine	.542	<.001*		
Oxycodone	.689	>.999	.002*	
Other	.197	<.001*	>.999	<.001*

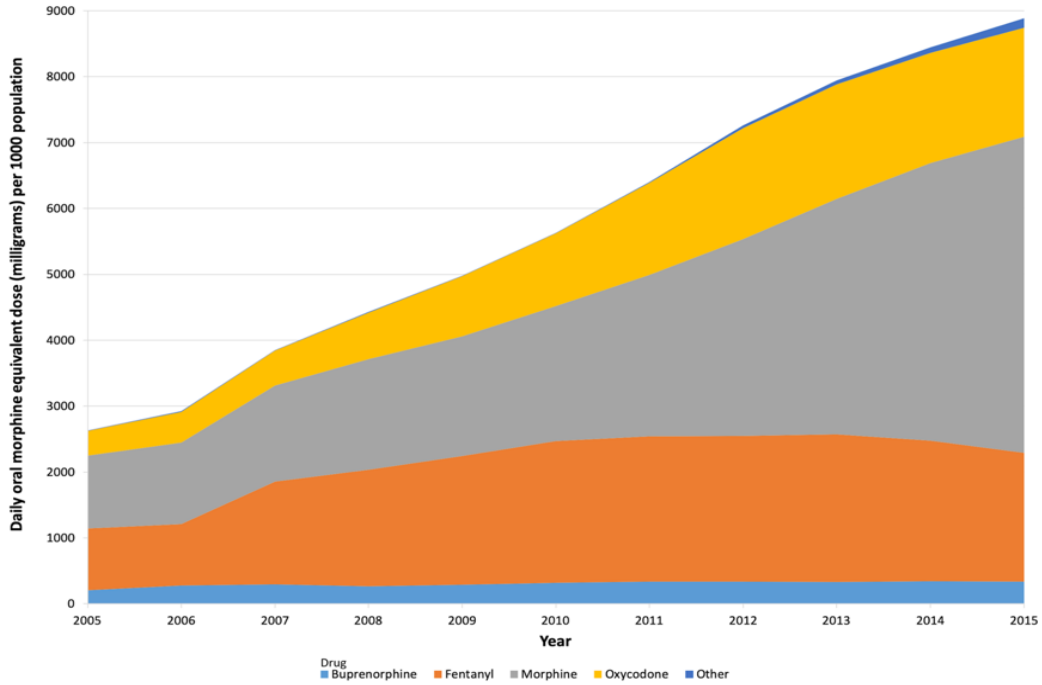


Figure D.D.4: Trends in oral morphine equivalent dose for preparations of 120 milligrams or more per day between 2005 – 2015

The differences between all 5 groups of opioids being prescribed at doses of 120 milligram $OMEQ_e$ per 1000 population or higher, were deemed significantly different overall (Kruskal-Wallis $p<.001$, $\eta^2= 0.835$. $d_{Cohen}= 4.49$). Post-hoc tests confirmed morphine, fentanyl and oxycodone were prescribed at higher $OMEQ_e$ pe 1000 population than was seen for 'other' opioids. Buprenorphine $OMEQ_e$ was significantly lower than observed for morphine and fentanyl (Table D.14).

There was little change in the $OMEQ_e$ per prescription for most products being prescribed at 120mg $OMEQ_e$ per day or higher during the study period (Table D.15Whilst morphine $OMEQ_e$ above 120 milligrams per day increased in total, the $OMEQ_e$ per prescription reduced by 4.9% over the 11 years examined (from 134 to 127 milligrams per prescription) (**Error! Reference source not found.**).

Table D.15: Trends in annual totals for preparations of 120mg or greater oral morphine equivalent dose in milligrams per prescription, stratified by drug and with rate change for 2005 - 2015

Year	Annual total daily oral morphine equivalent dose (milligrams) per prescription				
	Buprenorphine	Fentanyl	Morphine	Oxycodone	Other
2005	136	247	134	186	133
2006	137	254	132	187	132
2007	138	256	133	179	137
2008	139	257	132	181	139

2009	139	259	132	178	139
2010	139	258	132	178	135
2011	139	256	130	182	134
2012	138	257	130	184	138
2013	138	260	129	183	137
2014	132	259	129	183	141
2015	139	259	127	184	142
Rate change (%) 2005-2015	2.5	5.0	-4.9	-1.6	6.5

D.3 Gender differences in $OMEQ_e$

D.3.1 Gender differences in total OMEQe

Table D.16: Trends in Total Annualised Oral Morphine Equivalent Doses (milligrams) issued by gender. p-values calculated using Mann-Whitney tests for each drug

Year	Oral morphine equivalent dose (milligrams) prescribed								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
Men									
2005	410156	4953639	1902306	858765	1497950	636990	3071205	1155759	14486770
2006	553876	5526777	1862508	1252790	1672290	736160	3627890	385029	15617320
2007	615768	6208104	1875812	1615830	1985740	831980	4139380	223934	17496548
2008	649328	6826073	1866868	1862430	2278280	1049740	4566795	173936	19273450
2009	734270	7392070	1822380	1948750	2480120	1428840	5118830	163333	21088593
2010	831594	7926231	1758474	2162280	2842270	1796480	5674415	154301	23146045
2011	951130	8509375	1723444	2242295	3328020	2370360	6256045	151642	25532311
2012	1006858	8967529	1647382	2355650	4129530	2986980	6761750	168242	28023921
2013	993264	9180250	1596988	2432115	5027900	2945700	6872275	179737	29228229
2014	1008324	9589378	1561302	2450740	5968060	2715820	6565515	197031	30056170
2015	1010378	9966759	1508154	2323820	6901450	2750220	5874980	300065	30635826
Percentage change (%) 2005 – 2015	146.3	101.2	-20.7	170.6	360.7	331.8	91.3	-74.0	111.5
Women									
2005	567,521	8,464,725	2718324	1845875	1786660	706360	4790320	2301069	23180854
2006	744,082	9285911	2703070	2495755	2082840	897100	5682840	692086	24583684
2007	912,964	10263965	2708530	3060765	2527370	1128480	6406775	396822	27405671
2008	1,068,306	11182682	2643696	3574800	2964500	1587080	7048370	274114	30343548
2009	1,293,608	11887410	2535468	4096445	3305210	2027300	7681345	246856	33073642
2010	1,507,890	12582425	2462980	4514840	3825150	2427660	8264385	238749	35824079
2011	1,645,450	13319193	2418790	4723420	4785570	2909080	8937755	223636	38962894
2012	1,665,008	13964249	2327298	4768920	5953530	3177540	9518740	257008	41632293
2013	1,641,454	14191389	2219490	4857705	7303890	3291120	9689350	312101	43506499
2014	1,675,210	14737768	2161744	4531275	8807770	3331380	9224230	311285	44780662
2015	1,662,030	15253761	2083666	4172450	10190020	3415180	8378345	402382	45557834
Percentage change (%) 2005 – 2015	192.	80.2	-23.3	126.0	470.3	383..5	74.9	-82.5	96.5
Mann-Whitney p-value*, η^2, d_{Cohen}	<0.010*, 0.321, 1.377	<.001*, 0.561, 2.261	<.001*,0.717, 3.187	<.001*, 0.540, 2.168	0.217, 0.075, 0.586	0.243, 0.067, 0.536	<0.010*, 0.406, 1.653	<0.050*, 0.261, 1.189	

*p-value <0.05 = statistically significant

Table D.17: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the annualised daily oral morphine equivalent doses prescribed to men, by drug

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	<.001*						
Dihydrocodeine	>.999	.003*					
Fentanyl	.570	.017*	>.999				
Morphine	.009*	.877	>.999	>.999			
Oxycodone	>.999	.004*	>.999	>.999	>.999		
Tramadol	<.001*	>.999	.065	.291	>.999	.093	
Other	>.999	<.001*	.408	.027*	<.001*	.095	<.001*

*p-value < .05 = statistically significant

Table D.18: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the annualised daily oral morphine equivalent doses prescribed to women, by drug

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	<.001*						
Dihydrocodeine	>.999	.001*					
Fentanyl	.061	.161	>.999				
Morphine	.038*	.246	>.999	>.999			
Oxycodone	>.999	<.001*	>.999	>.999	>.999		
Tramadol	<.001*	>.999	.067	>.999	>.999	.023	
Other	>.999	<.001*	.212	.002*	.001*	.509	<.001*

*p-value < .05 = statistically significant

D.3.2 Gender differences in OMEQe per 1000 population

Table D.19: Trends in Total Annualised Oral Morphine Equivalent Doses (milligrams) per 1000 population issued by gender. p-values calculated using Mann-Whitney tests for each drug

Year	Oral morphine equivalent dose (milligrams) per 1000 population							
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other

Men								
2005	363	4388	1685	761	1327	564	2720	1024
2006	488	4869	1641	1104	1473	649	3196	339
2007	538	5421	1638	1411	1734	727	3615	196
2008	563	5917	1618	1614	1975	910	3959	151
2009	634	6385	1574	1683	2142	1234	4421	141
2010	714	6810	1511	1858	2442	1543	4875	133
2011	812	7266	1472	1915	2842	2024	5342	129
2012	857	7629	1401	2004	3513	2541	5752	143
2013	842	7781	1354	2062	4262	2497	5825	152
2014	851	8095	1318	2069	5038	2292	5542	166
2015	850	8389	1269	1956	5809	2315	4945	253
Rate change (%) 2005 – 2015	134.1	91.2	-24.7	157.1	337.8	310.2	81.8	-75.3
Women								
2005	478	7134	2291	1556	1506	595	4037	1939
2006	624	7783	2266	2092	1746	752	4763	580
2007	761	8559	2259	2552	2108	941	5343	331
2008	886	9273	2192	2964	2458	1316	5845	227
2009	1072	9849	2101	3394	2738	1680	6364	205
2010	1246	10400	2036	3732	3162	2007	6831	197
2011	1356	10973	1993	3892	3943	2397	7364	184
2012	1367	11468	1911	3916	4889	2609	7817	211
2013	1345	11630	1819	3981	5986	2697	7941	256
2014	1370	12049	1767	3705	7201	2724	7542	254
2015	1356	12447	1700	3405	8315	2787	6837	328
Rate change (%) 2005 – 2015	183.5	74.5	-25.8	118.8	452.2	368.1	69.3	-83.1
p-value (Mann-Whitney)	.010*	<.001*	<.001*	<.001*	.332	.270	.004*	.019*

*p-value < .05 = statistically significant

Table D.20: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the annualised daily oral morphine equivalent doses prescribed to men per 1000 population, by drug

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol

Codeine	<.001*						
Dihydrocodeine	>.999	0.003*					
Fentanyl	0.570	0.017*	>.999				
Morphine	0.009*	0.877	>.999	>.999			
Oxycodone	>.999	0.004*	>.999	>.999	>.999		
Tramadol	<.001*	>.999	0.065	0.291	>.999	0.093	
Other	>.999	<.001*	0.408	0.027*	<.001*	0.095	<.001*

*p-value < .05 = statistically significant

Table D.21: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the annualised daily oral morphine equivalent doses prescribed to women per 1000 population, by drug

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	<.001*						
Dihydrocodeine	>.999	<.001*					
Fentanyl	0.061	0.161	>.999				
Morphine	0.038*	0.246	>.999	>.999			
Oxycodone	>.999	<.001*	>.999	>.999	>.999		
Tramadol	<.001*	>.999	0.067	>.999	>.999	0.023	
Other	>.999	<.001*	0.212	0.002*	.001*	0.509	<.001*

*p-value < .05 = statistically significant

D.3.3 Gender differences in OMEQe per prescription

Table D.22: Trends in oral morphine equivalent dose (milligrams) per prescription issued and by drug, stratified by gender. p-values calculated using Mann-Whitney tests

	Oral morphine equivalent dose (milligrams) per prescription issued								
	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol	Other	Total
Men									
2005	98	17	13	187	89	113	36	27	24
2006	85	17	13	187	90	115	36	29	25
2007	67	17	13	181	90	106	37	30	26
2008	55	18	13	175	88	102	37	30	27

2009	50	18	13	174	85	101	37	31	28
2010	47	18	13	172	84	102	38	31	29
2011	47	18	13	173	81	106	38	33	30
2012	46	19	13	169	78	113	38	37	31
2013	46	19	13	168	75	114	38	42	32
2014	47	19	14	171	73	112	38	49	32
2015	46	20	14	169	71	110	38	60	33
Percentage change (%) 2005 – 2015	-53.0	14.9	4.7	-9.4	-20.0	-2.8	6.1	124.0	34.3
Women									
2005	97	16	12	187	83	102	36	26	23
2006	69	16	12	175	80	97	36	28	24
2007	53	17	12	164	81	95	37	29	25
2008	42	17	12	158	81	96	37	30	26
2009	38	17	12	156	79	93	37	30	27
2010	36	18	12	155	76	91	38	30	28
2011	35	18	13	149	75	92	38	32	29
2012	34	18	13	145	73	93	38	38	30
2013	33	18	13	144	69	95	38	43	30
2014	32	19	13	140	68	95	38	48	31
2015	32	19	13	137	66	93	38	56	31
Percentage change (%) 2005 – 2015	-67.0	17.2	6.2	-26.8	-19.9	-9.1	5.5	113.2	35.4
Mann-Whitney p-value	.023*	.217	.010*	.003*	.040*	<.001	.797	.652	.365

*p-value < .05 = statistically significant

Table D.23: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the annualised daily oral morphine equivalent doses prescribed per prescription to men, by drug

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	.062						
Dihydrocodeine	.001*	>.999					
Fentanyl	.075	<.001*	<.001*				
Morphine	>.999	.003*	<.001*	.845			
Oxycodone	>.999	<.001*	<.001*	>.999	>.999		

Tramadol	>.999	>.999	.179	<.001*	.819	.024*	
Other	>.999	>.999	.408	<.001*	.385	.008*	>.999

*p-value < .05 = statistically significant

Table D.24: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between the annualised daily oral morphine equivalent doses prescribed per prescription to women, by drug

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	.0479						
Dihydrocodeine	.019*	>.999					
Fentanyl	.007*	<.001*	<.001*				
Morphine	>.999	.002*	<.001*	.920			
Oxycodone	.269	<.001*	<.001*	>.999	>.999		
Tramadol	>.999	.690	.031*	.004*	>.999	.179	
Other	>.999	>.999	.236	<.001*	.592	.023*	>.999

*p-value < .05 = statistically significant

D.3.4 Gender differences for high dose opioid prescription

Table D.25: Gender trends for preparations of 120mg or greater oral morphine equivalent dose in milligrams

		Annual total daily oral morphine equivalent dose (milligrams)				
		Buprenorphine	Fentanyl	Morphine	Oxycodone	Other
Men						
	2005	208064	716295	1190320	455090	31560
	2006	293336	1026620	1308560	526360	29908
	2007	312280	1303620	1562600	559480	17760
	2008	273544	1489020	1745000	686200	15656
	2009	299160	1558840	1880740	943880	16212
	2010	329280	1731300	2127520	1189600	18500
	2011	368088	1784600	2453950	1607760	22788
	2012	389216	1842920	2983340	2116360	37516
	2013	392024	1885260	3553150	2108560	55292
	2014	420168	1927465	4169900	1953280	81072

2015	412976	1812410	4741300	1933280	160644
Percentage change (%) 2005 – 2015	153.0	153.0	298.3	324.8	409.0
Women					
2005	266744	1488620	1352540	456000	26264
2006	350040	1963720	1568920	563640	25560
2007	382624	2352240	1882450	692840	20776
2008	349024	2685600	2226160	972920	16768
2009	390176	3051200	2427070	1215360	13472
2010	431760	3373640	2780800	1436160	18232
2011	435664	3467620	3388520	1731760	26040
2012	416688	3443100	4218870	1912560	67476
2013	400888	3490920	5038100	2059480	98016
2014	410800	3207780	5976730	2076560	120632
2015	404928	2899880	6857400	2070120	192352
Percentage change (%) 2005 – 2015	51.8	94.8	407.0	354.0	632.4
p-value (Mann-Whitney)	.088	<.001*	.217	.748	.847

Between 2005 and 2015, 63,059,624 milligrams $OMEQ_e$ were prescribed for men and 89,194,204 milligrams $OMEQ_e$ to women using products with a total daily dose of 120mg $OMEQ_e$ or higher (when prescribed at recommended doses). This equates to 24.8% of $OMEQ_e$ prescribed over the study period, coming from formulations with a potential daily dose of 120mg morphine-equivalent or higher.

Table D.26: Gender trends in annual totals for preparations of 120mg or greater oral morphine equivalent dose in milligrams and adjusted to oral morphine equivalent dose per 1000 gender-adjusted population, stratified by drug and with percentage and rate change for 2005 - 2015

	Annual total daily oral morphine equivalent dose (milligrams) per 1000 population				
Year	Buprenorphine	Fentanyl	Morphine	Oxycodone	Other
Men					
2005	184	634	1054	403	28
2006	258	904	1153	464	26
2007	273	1138	1365	489	16

2008	237	1291	1513	595	14
2009	258	1346	1624	815	14
2010	283	1487	1828	1022	16
2011	314	1524	2095	1373	19
2012	331	1568	2538	1800	32
2013	332	1598	3012	1787	47
2014	355	1627	3520	1649	68
2015	348	1525	3991	1627	135
Rate change (%)2005 – 2015	89.1	140.4	278.5	303.7	383.7
Women					
2005	225	1255	1140	384	22
2006	293	1646	1315	472	21
2007	319	1962	1570	578	17
2008	289	2227	1846	807	14
2009	323	2528	2011	1007	11
2010	357	2788	2298	1187	15
2011	359	2857	2792	1427	21
2012	342	2828	3465	1571	55
2013	329	2861	4129	1688	80
2014	336	2623	4886	1698	99
2015	330	2366	5596	1689	157
Rate change (%) 2005 – 2015	47.0	88.6	390.9	339.5	609.1
Mann-Whitney p-value*	0.193	<.001*	0.332	>.999	0.949

*p-value < .05 = statistically significant

The total daily $OMEQ_e$ of 120mg or above derived increased for both genders during the study period (Figure D.5). The smallest increase was noted from buprenorphine products (Table D.27) although still nearly doubled for men (from 208,064 to 412,976 milligrams, 98.5% increase) and increased by just over half for women (from 266,744 to 404,928 milligrams, 51.8% increase).

Whilst not statistically significant (Table D.27), the difference between the $OMEQ_e$ of morphine over 120mg daily received by women and men increased over the 11 years examined. In 2005, women received prescriptions of approximately 14% more $OMEQ_e$ than men (1,352,540 versus 1,190,320 milligrams respectively). In 2015, that had increased to a 45% difference in milligrams morphine prescribed (6,857,400 versus 4,741,300 milligrams respectively) (Figure D.5). The average difference between women and men in the $OMEQ_e$ from preparations of 120mg daily $OMEQ_e$ and above, over the study period was 36% (27,716,380 versus 37,717,560 milligrams respectively).

Table D.27: Gender trends for preparations of 120mg or greater oral morphine equivalent dose per 1000 gender-adjusted population, stratified by drug and with rate change

	Annual total daily oral morphine equivalent dose (milligrams) per prescription				
Year	Buprenorphine	Fentanyl	Morphine	Oxycodone	Other
Men					
2005	136	237	135	186	126
2006	138	258	136	195	126
2007	139	261	139	187	127
2008	139	262	136	182	127
2009	139	262	136	181	130
2010	138	261	137	180	128
2011	138	266	134	184	135
2012	138	272	133	187	137
2013	139	274	132	185	137
2014	126	278	131	183	141
2015	139	282	130	185	141
Percentage change (%) 2005 – 2015	2.2	19.0	-3.7	-0.9	12.2
Women					
2005	135	252	133	187	144
2006	136	251	129	180	140
2007	137	254	128	173	146
2008	139	254	129	181	152
2009	139	257	129	177	151
2010	139	257	129	176	142
2011	139	251	128	179	133
2012	138	250	128	182	138
2013	138	253	127	182	137
2014	138	248	127	183	140
2015	139	247	126	182	143
Rate change (%) 2005 – 2015	2.7	-2.1	-5.5	-2.3	-0.6
p-value (Mann-Whitney)	0.847	<.001*	<.001*	0.171	<.001*

*p-value < .05 = statistically significant

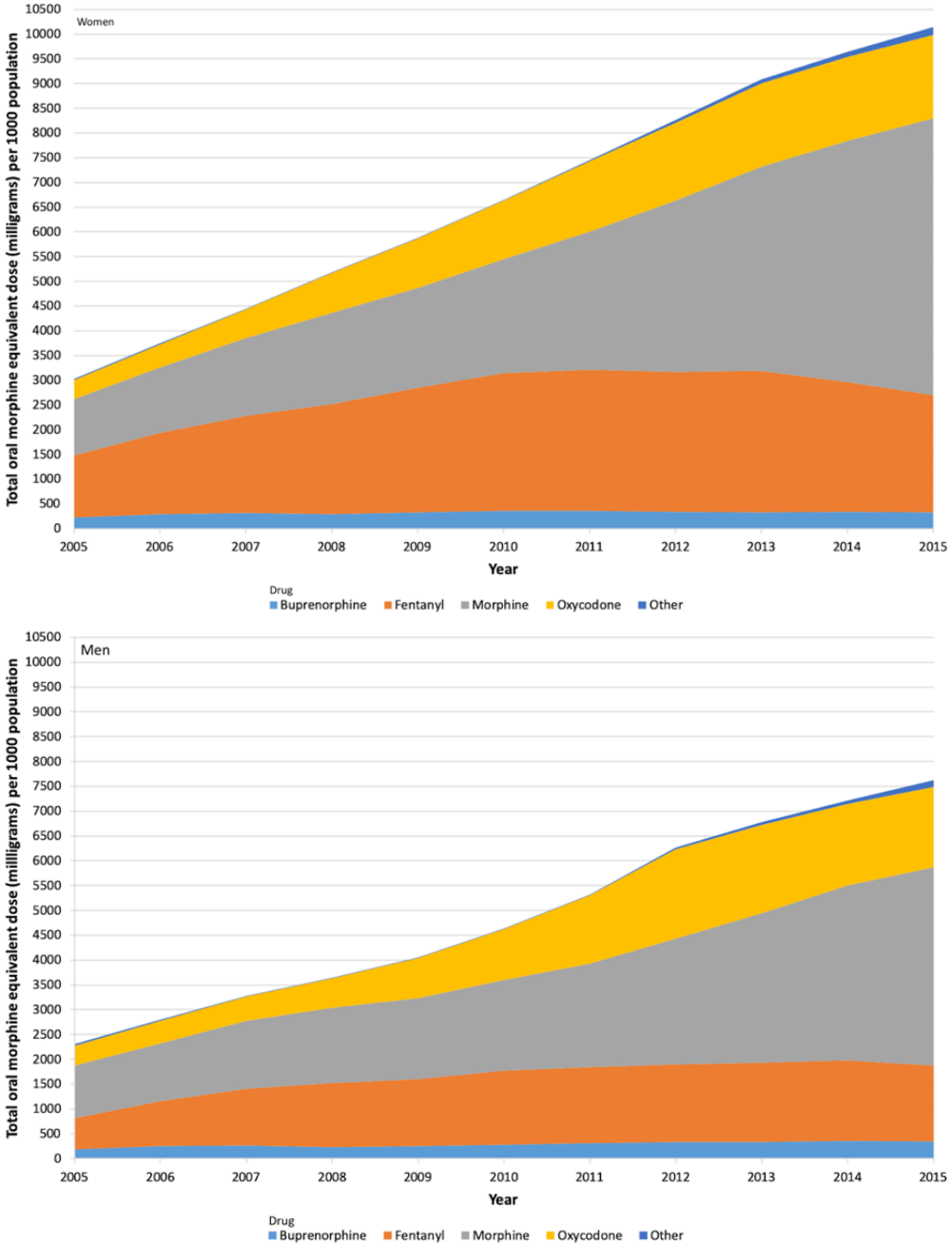


Figure D.5: Trends in Oral Morphine Equivalent Dose (milligrams) per prescription issued with products with 120mg OME and greater and stratified by drug. Examined by gender (Top – men, bottom – women)

Fentanyl $OMEQ_e$ increased for both genders (Table C.28) and whilst not the largest increase seen over the study period, was the only $OMEQ_e$ category with a statistically significant difference between genders ($p<.001$), when subjected to Mann-Whitney analysis.

Oral morphine equivalent dose per prescription appeared Fentanyl and morphine $OMEQ_e$s per prescription were higher for men ($p<.005$ and $p<.001$ respectively) and 'other' opioid $OMEQ_e$s were higher for women ($p<.001$*). Buprenorphine demonstrated a small increase in $OMEQ_e$ per prescription for high-dose preparations for men and women. High-dose $OMEQ_e$ per prescription

reduced for all other categories for women although increased for fentanyl and 'other' opioids for men over the same time period (Table D.27)

D.4 $OMEQ_e$ in areas of socioeconomic deprivation

D.4.1 Total OMEQe by quintile of deprivation

Table D.28: Trends in total oral morphine equivalent dose prescribed stratified by deprivation (Welsh Index of Multiple Deprivation) and adjusted to population.

Year	Oral morphine equivalent dose (milligrams) prescribed				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	10,319,636	8,590,375	7,684,060	5,374,595	4,486,035
2006	11,002,416	9,234,855	8,203,320	5,758,390	4,925,110
2007	12,215,442	10,384,487	9,027,524	6,499,993	5,474,191
2008	13,795,845	11,098,955	9,780,820	7,300,944	6,032,501
2009	15,060,880	12,151,599	10,743,046	8,084,842	6,469,233
2010	16,120,158	13,438,172	11,745,722	8,774,296	7,069,176
2011	17,575,890	14,766,808	12,985,192	9,525,368	7,586,660
2012	18,971,106	16,079,570	14,242,512	10,133,897	8,162,570
2013	19,953,808	16,327,490	14,955,099	10,546,332	8,563,467
2014	20,641,165	16,988,538	15,170,432	10,814,134	8,622,456
2015	21,167,919	17,399,026	15,342,942	10,878,897	8,721,170
Percentage change (%) 2005 – 2015	105.1	102.5	99.7	102.4	94.4
Total prescribed 2005-2015	176,824,265	146,459,878	129,880,669	93,691,687	76,112,569

WIMD1 = most deprived, WIMD5 = least deprived

Table D.29: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the oral morphine equivalent doses prescribed in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	0.537	>.999		
4	.001*	0.052	0.504	
5	<.001*	<.001*	0.017*	>.999

*p-value < .05 = statistically significant, WIMD1 = most deprived, WIMD5 = least deprived

D.4.2 OMEQe per 1000 population and by deprivation quintile

Table D.30: Trends in total oral morphine equivalent dose prescribed stratified by deprivation (Welsh Index of Multiple Deprivation) and adjusted to population

Year	Estimated oral morphine equivalent dose (milligrams) per 1000 population				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	21,757	18,203	17,108	12,242	9,381
2006	23,069	19,461	18,164	13,044	10,243
2007	25,436	21,734	19,852	14,624	11,307
2008	28,541	23,079	21,369	16,319	12,379
2009	31,419	25,247	23,211	17,805	13,349
2010	33,488	27,826	25,291	19,260	14,518
2011	36,340	30,451	27,838	20,816	15,496
2012	39,085	33,047	30,433	22,075	16,607
2013	40,982	33,472	31,879	22,917	17,361
2014	42,237	34,720	32,250	23,432	17,413
2015	43,176	35,475	32,564	23,534	17,557
Rate change (%) 2005-2015	98.4	94.9	90.3	92.2	87.2

WIMD1 = most deprived, WIMD5 = least deprived

Table D.31: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the oral morphine equivalent doses per 1000 population prescribed in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	0.790	>.999		
4	0.003*	0.119	0.570	
5	<.001*	<.001*	0.005*	>.999

*p-value < .05 = statistically significant, WIMD1 = most deprived, WIMD5 = least deprived

D.4.3 OMEQe per prescription and per person

Table D.32: Trends in oral morphine equivalence stratified by deprivation (Welsh Index of Multiple Deprivation WIMD2011) and examined by dose per prescription and dose per person

Year	Oral morphine equivalent dose (milligrams) per prescription				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	22	24	24	25	24
2006	23	25	25	26	25
2007	24	26	26	27	26
2008	25	26	27	28	26
2009	26	27	28	29	27
2010	27	28	29	30	28
2011	28	29	30	31	28
2012	29	31	32	31	29
2013	30	31	33	32	30
2014	31	32	32	32	30
2015	31	32	33	33	30
Rate change (%) 2005 – 2015	41.0	36.3	33.1	28.9	27.9
	Oral morphine equivalent dose (milligrams) per person receiving prescriptions				
2005	96	99	98	93	80
2006	104	107	104	99	87
2007	109	113	107	102	89
2008	119	116	110	108	93
2009	126	123	118	116	96
2010	131	131	123	120	102
2011	141	141	134	128	107
2012	150	151	147	136	115
2013	160	157	156	144	124
2014	166	164	158	148	125
2015	173	169	161	151	128
Rate change (%) 2005 – 2015	79.2	70.2	64.7	61.3	60.2

WIMD1 = most deprived, WIMD5 = least deprived

Table D.33: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number people receiving opioid prescriptions in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	>.999	>.999	>.999	
5	.046*	.048*	.191	.745

*p-value < .05 = statistically significant WIMD1=most deprived, WIMD5-least deprived

D.4.4 High dose prescribing by deprivation quintile

Table D.34: Trends in total oral morphine equivalent dose of 120 milligrams or higher prescribed stratified by deprivation (Welsh Index of Multiple Deprivation)

Year	Oral morphine equivalent dose for doses of 120 milligrams per day and over				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	1,466,652	1,208,800	1,373,446	1,104,120	697,496
2006	1,860,742	1,779,300	1,674,320	1,319,344	969,624
2007	2,157,344	2,285,544	1,941,096	1,537,720	1,140,146
2008	2,718,216	2,470,438	2,128,180	1,822,578	1,201,084
2009	3,072,296	2,288,286	2,440,202	2,133,356	1,289,852
2010	3,263,196	2,759,170	2,829,734	2,405,498	1,525,984
2011	3,691,928	3,071,124	3,338,804	2,639,240	1,670,600
2012	4,223,200	3,622,164	4,000,144	2,841,846	1,895,168
2013	4,665,156	3,858,312	4,476,098	3,099,268	2,162,012
2014	5,150,352	4,442,212	4,499,933	3,202,667	2,178,040
2015	5,674,237	4,837,285	4,642,419	3,314,817	2,228,629
Percentage change (%)2005 – 2015	286.9	300.2	238.0	200.2	219.5
Total prescribed 2005-2015	37,943,319	32,622,635	33,344,376	25,420,454	16,958,635

WIMD1 = most deprived, WIMD5 = least deprived

Table D.35: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between OMEQe from products with >120mg OMEQe daily dose, in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	.663	>.999	>.999	
5	.002	.023	.022	.643

*p-value < .05 = statistically significant, WIMD1=most deprived, WIMD5=least deprived

Table D.36: Trends in total oral morphine equivalent dose of 120 milligrams or higher prescribed stratified by deprivation (Welsh Index of Multiple Deprivation) and adjusted to deprivation quintile population

Year	Total oral morphine equivalent dose per 1000 population for products of over 120mg $OMEQ_e$				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
2005	3,092	2,,561	3,058	2,515	1,459
2006	3,901	3,750	3,707	2,989	2,017
2007	4,492	4,784	4,268	3,460	2,355
2008	5,624	5,137	4,650	4,074	2,465
2009	6,409	4,754	5,272	4,698	2,662
2010	6,779	5,713	6,093	5,280	3,134
2011	7,633	6,333	7,158	5,768	3,412
2012	8,701	7,444	8,547	6,190	3,856
2013	9,581	7,910	9,541	6,735	4,383
2014	10,539	9,079	9,566	6,940	4,399
2015	11,574	9,863	9,853	7,171	4,487
Rate change (%) 2005 – 2015	274.3	285.0	222.2	185.1	207.6

WIMD1 = most deprived, WIMD5 = least deprived

Table D.37: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between OMEQe from products with >120mg OMEQe daily dose per 1000 population, in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4

2	>.999			
3	>.999	>.999		
4	>.999	>.999	>.999	
5	<.001*	.013*	.009*	.098

*p-value < .05 = statistically significant WIMD1=most deprived, WIMD5-least deprived

Appendix E Time Series Analysis examining the effect of legislation and prescribing guidance on opioid prescribing in Wales

E.1 Schedules of controlled drugs in the UK

E.1.1 Schedule 1 controlled drugs

Subject to the requirements of regulations 14, 15, 16, 18, 19, 20, 23, 26 and 27 (legislation.gov.uk and UK Government 2021)

1. The following substances and products, namely -

(a)Bufotenine

- Cannabinol
- Cannabinol derivatives not being dronabinol or its stereoisomers
- Cannabis and cannabis resin
- Cathinone
- Coca leaf
- Concentrate of poppy-straw
- Eticyclidine
- Etryptamine
- Lysergamide
- Lysergide and other *N*-alkyl derivatives of lysergamide
- Mescaline
- Methcathinone
- Psilocin
- Raw opium
- Rolicyclidine
- Tenocyclidine
- 4-Bromo-2,5-dimethoxy-a-methylphenethylamine
- *N,N*-Diethyltryptamine
- *N,N*-Dimethyltryptamine
- 2,5-Dimethoxy-α,4-dimethylphenethylamine
- *N*-Hydroxy-tenamphetamine
- 4-Methyl-aminorex

(b)any compound (not being a compound for the time being specified in sub-paragraph (a) above) structurally derived from tryptamine or from a ring-hydroxy tryptamine by substitution at the nitrogen atom of the sidechain with one or more alkyl substituents but no other substituent;

(c)the following phenethylamine derivatives, namely—

- Allyl(α-methyl-3,4-methylenedioxyphenethyl)amine
- 2-Amino-1-(2,5-dimethoxy-4-methylphenyl)ethanol
- 2-Amino-1-(3,4-dimethoxyphenyl)ethanol
- Benzyl(α-methyl-3,4-methylenedioxyphenethyl)amine
- 4-Bromo-*β*,2,5-trimethoxyphenethylamine
- *N*-(4-*sec*-Butylthio-2,5-dimethoxyphenethyl)hydroxylamine
- Cyclopropylmethyl(α-methyl-3,4-methylenedioxyphenethyl)amine
- 2-(4,7-Dimethoxy-2,3-dihydro-1H-indan-5-yl)ethylamine
- 2-(4,7-Dimethoxy-2,3-dihydro-1H-indan-5-yl)-1-methylethylamine
- 2-(2,5-Dimethoxy-4-methylphenyl)cyclopropylamine
- 2-(1,4-Dimethoxy-2-naphthyl)ethylamine
- 2-(1,4-Dimethoxy-2-naphthyl)-1-methylethylamine
- *N*-(2,5-Dimethoxy-4-propylthiophenethyl)hydroxylamine
- 2-(1,4-Dimethoxy-5,6,7,8-tetrahydro-2-naphthyl)ethylamine
- 2-(1,4-Dimethoxy-5,6,7,8-tetrahydro-2-naphthyl)-1-methylethylamine

- α, α-Dimethyl-3,4-methylenedioxyphenethylamine
- α,α-Dimethyl-3,4-methylenedioxyphenethyl(methyl)amine
- Dimethyl(α-methyl-3,4-methylenedioxyphenethyl)amine
- *N*-(4-Ethylthio-2,5-dimethoxyphenethyl)hydroxylamine
- 4-Iodo-2,5-dimethoxy-a-methylphenethyl(dimethyl)amine
- 2-(1,4-Methano-5,8-dimethoxy-1,2,3,4-tetrahydro-6-naphthyl)ethylamine
- 2-(1,4-Methano-5,8-dimethoxy-1,2,3,4-tetrahydro-6-naphthyl)-1-methylethylamine
- 2-(5-Methoxy-2,2-dimethyl-2,3-dihydrobenzo[*b*]furan-6-yl)-1-methylethylamine
- 2-Methoxyethyl(α-methyl-3,4-methylenedioxyphenethyl)amine
- 2-(5-Methoxy-2-methyl-2,3-dihydrobenzo[*b*]furan-6-yl)-1-methylethylamine
- β-Methoxy-3,4-methylenedioxyphenethylamine
- 1-(3,4-Methylenedioxybenzyl)butyl(ethyl)amine
- 1-(3,4-Methylenedioxybenzyl)butyl(methyl)amine
- 2-(α-Methyl-3,4-methylenedioxyphenethylamino)ethanol
- α-Methyl-3,4-methylenedioxyphenethyl(prop-2-ynyl)amine
- *N*-Methyl-*N*-(α-methyl-3,4-methylenedioxyphenethyl)hydroxylamine
- *O*-Methyl-*N*-(α-methyl-3,4-methylenedioxyphenethyl)hydroxylamine
- α-Methyl-4-(methylthio)phenethylamine
- β,3,4,5-Tetramethoxyphenethylamine
- β,2,5-Trimethoxy-4-methylphenethylamine

(d)any compound (not being methoxyphenamine or a compound for the time being specified in sub-paragraph (a) above) structurally derived from phenethylamine, an *N*-alkylphenethylamine, α-methylphenethylamine, an *N*-alkyl-α-methylphenethylamine, α-ethylphenethylamine, or an *N*-alkyl-α-ethylphenethylamine by substitution in the ring to any extent with alkyl, alkoxy, alkylenedioxy or halide substitutents, whether or not further substituted in the ring by one or more other univalent substituents;

(e)any compound (not being a compound for the time being specified in Schedule 2) structurally derived from fentanyl by modification in any of the following ways, that is to say -

(i)by replacement of the phenyl portion of the phenethyl group by any heteromonocycle whether or not further substituted in the heterocycle;

(ii)by substitution in the phenethyl group with alkyl, alkenyl, alkoxy, hydroxy, halogeno, haloalkyl, amino or nitro groups;

(iii)by substitution in the piperidine ring with alkyl or alkenyl groups;

(iv)by substitution in the aniline ring with alkyl, alkoxy, alkylenedioxy, halogeno or haloalkyl groups;

(v)by substitution at the 4-position of the piperidine ring with any alkoxycarbonyl or alkoxyalkyl or acyloxy group;

(vi)by replacement of the *N*-propionyl group by another acyl group;

(f)any compound (not being a compound for the time being specified in Schedule 2) structurally derived from pethidine by modification in any of the following ways, that is to say—

(i)by replacement of the l-methyl group by an acyl, alkyl whether or not unsaturated, benzyl or phenethyl group, whether or not further substituted;

(ii)by substitution in the piperidine ring with alkyl or alkenyl groups or with a propano bridge, whether or not further substituted;

(iii)by substitution in the 4-phenyl ring with alkyl, alkoxy, aryloxy, halogeno or haloalkyl groups;

(iv)by replacement of the 4-ethoxycarbonyl by any other alkoxycarbonyl or any alkoxyalkyl or acyloxy group;

(v)by formation of an N-oxide or of a quaternary base.

2. Any stereoisomeric form of a substance specified in paragraph 1.

3. Any ester or ether of a substance specified in paragraph 1 or 2.

4. Any salt of a substance specified in any of paragraphs 1 to 3.

5. Any preparation or other product containing a substance or product specified in any of paragraphs 1 to 4, not being a preparation specified in Schedule 5.

E.1.2 Schedule 2 controlled drugs

Subject to the requirements of regulations 14, 15, 16, 18, 19, 20, 21, 23, 26 and 27

1. The following substances and products, namely—

Acetorphine

Alfentanil

Allylprodine

Alphacetylmethadol

Alphameprodine

Alphamethadol

Alphaprodine

Anileridine

Benzethidine

Benzylmorphine (3-benzylmorphine)

Betacetylmethadol

Betameprodine

Betamethadol

Betaprodine

Bezitramide

Carfentanil

Clonitazene

Cocaine

Desomorphine

Dextromoramide

Diamorphine

Diampromide

Diethylthiambutene

Difenoxin

Dihydrocodeinone

O-carboxymethyloxime

Dihydromorphine

Dimenoxadole

Levomoramide

Levophenacylmorphan

Levorphanol

Lofentanil

Medicinal opium

Metazocine

Methadone

Methadyl acetate

Methyldesorphine

Methyldihydromorphine

(6-methyldihydromorphine)

Metopon

Morpheridine

Morphine

Morphine methobromide, morphine N-oxide and

other pentavalent nitrogen morphine derivatives

Myrophine

Nicomorphine

Noracymethadol

Norlevorphanol

Normethadone

Normorphine

Norpipanone

Oxycodone

Oxymorphone

Pethidine

Phenadoxone

Phenampromide

Dimepheptanol

Dimethylthiambutene

Dioxaphetyl butyrate

Diphenoxylate

Dipipanone

Dronabinol

Drotebanol

Ecgonine, and any derivative of ecgonine which is convertible to ecgonine or to cocaine

Ethylmethylthiambutene

Etonitazene

Etorphine

Etoxeridine

Fentanyl

Furethidine

Hydrocodone

Hydromorphinol

Hydromorphone

Hydroxypethidine

Isomethadone

Ketobemidone

Levomethorphan

Phenazocine

Phencyclidine

Phenomorphan

Phenoperidine

Piminodine

Piritramide

Proheptazine

Properidine

Racemethorphan

Racemoramide

Racemorphan

Sufentanil

Thebacon

Thebaine

Tilidate

Trimeperidine

Zipeprol

4-Cyano-2-dimethylamino-4,4-diphenylbutane

4-Cyano-1-methyl-4-phenylpiperidine

2-Methyl-3-morpholino-1,1-diphenylpropane-carboxylic acid

α-Methylphenethylhydroxylamine

1-Methyl-4-phenylpiperidine-4-carboxylic acid

4-Phenylpiperidine-4-carboxylic acid ethyl ester

2. Any stereoisomeric form of a substance specified in paragraph 1 not being dextromethorphan or dextrorphan.

3. Any ester or ether of a substance specified in paragraph 1 or 2, not being a substance specified in paragraph 6.

4. Any salt of a substance specified in any of paragraphs 1 to 3.

5. Any preparation or other product containing a substance or product specified in any of paragraphs 1 to 4, not being a preparation specified in Schedule 5.

6. The following substances and products, namely—

Acetyldihydrocodeine

Methaqualone

Amphetamine	Methylamphetamine
Codeine	Methylphenidate
Dextropropoxyphene	Nicocodine
Dihydrocodeine	Nicodicodine (6-nicotinoyldihydrocodeine)
Ethylmorphine (3-ethylmorphine)	Norcodeine
Fenethylline	Phenmetrazine
Glutethimide	Pholcodine
Lefetamine	Propiram
Mecloqualone	Quinalbarbitone

7. Any stereoisomeric form of a substance specified in paragraph 6.

8. Any salt of a substance specified in paragraph 6 or 7.

9. Any preparation or other product containing a substance or product specified in any of paragraphs 6 to 8, not being a preparation specified in Schedule 5.

E.1.3 Schedule 3 controlled drugs

Subject to the requirements of regulations 14, 15 (except temazepam), 16, 18, 22, 23, 24, 26 and 27

1. The following substances, namely—

Benzphetamine	Mephentermine
Buprenorphine	Meprobamate
Cathine	Methylphenobarbitone
Chlorphentermine	Methyprylone
Diethylpropion	Pentazocine
Ethchlorvynol	Phendimetrazine
Ethinamate	Phentermine
Flunitrazepam	Pipradrol
Mazindol	Temazepam

(b)any 5, 5 disubstituted barbituric acid not being quinalbarbitone.

2. Any stereoisomeric form of a substance specified in paragraph 1 not being phenylpropanolamine.

3. Any salt of a substance specified in paragraph 1 or 2.

4. Any preparation or other product containing a substance specified in any of paragraphs 1 to 3, not being a preparation specified in Schedule 5.

E.1.4 Schedule 4 Part I controlled drugs

Subject to the requirements of regulations 22, 23, 26 and 27

1. The following substances and products, namely—

Alprazolam	Ketazolam
Aminorex	Loprazolam
Bromazepam	Lorazepam
Brotizolam	Lormetazepam
Camazepam	Medazepam
Chlordiazepoxide	Mefenorex
Clobazam	Mesocarb
Clonazepam	Midazolam
Clorazepic acid	Nimetazepam
Clotiazepam	Nitrazepam
Cloxazolam	Nordazepam
Delorazepam	Oxazepam
Diazepam	Oxazolam
Estazolam	Pemoline
Ethyl loflazepate	Pinazepam
Fencamfamin	Prazepam
Fenproporex	Pyrovalerone
Fludiazepam	Tetrazepam
Flurazepam	Triazolam
Halazepam	*N*-Ethylamphetamine
Haloxazolam	

2. Any stereoisomeric form of a substance specified in paragraph 1.

3. Any salt of a substance specified in paragraph 1 or 2.

4. Any preparation or other product containing a substance or product specified in any of paragraphs 1 to 3, not being a preparation specified in Schedule 5.

Part ii controlled drugs excepted from the prohibition on possession when in the form of a medicinal product; excluded from the application of offences arising from the prohibition on importation and exportation when imported or exported in the form of a medicinal product by any person for administration to himself; and subject to the requirements of regulations 22, 23, 26 and 27

1. The following substances, namely—

Atamestane	Methenolone
Bolandiol	Methyltestosterone
Bolasterone	Metribolone
Bolazine	Mibolerone

Boldenone	Nandrolone
Bolenol	Norboletone
Bolmantalate	Norclostebol
Calusterone	Norethandrolone
4-Chloromethandienone	Ovandrotone
Clostebol	Oxabolone
Drostanolone	Oxandrolone
Enestebol	Oxymesterone
Epitiostanol	Oxymetholone
Ethyloestrenol	Prasterone
Fluoxymesterone	Propetandrol
Formebolone	Quinbolone
Furazabol	Roxibolone
Mebolazine	Silandrone
Mepitiostane	Stanolone
Mesabolone	Stanozolol
Mestanolone	Stenbolone
Mesterolone	Testosterone
Methandienone	Thiomesterone
Methandriol	Trenbolone

2. Any compound (not being Trilostane or a compound for the time being specified in paragraph 1 of this Part of this Schedule) structurally derived from 17-hydroxyandrostan-3-one or from 17-hydroxyestran-3-one by modification in any of the following ways, that is to say -

(a)by further substitution at position 17 by a methyl or ethyl group;

(b)by substitution to any extent at one or more of positions 1, 2, 4, 6, 7, 9, 11 or 16, but at no other position;

(c)by unsaturation in the carbocyclic ring system to any extent, provided that there are no more than two ethylenic bonds in any one carbocyclic ring;

(d)by fusion of ring A with a heterocyclic system.

3. Any substance which is an ester or ether (or, where more than one hydroxyl function is available, both an ester and an ether) of a substance specified in paragraph 1 or described in paragraph 2 of this Part of this Schedule.

4. The following substances, namely—

- Chorionic Gonadotrophin (HCG)
- Clenbuterol
- Non-human chorionic gonadotrophin
- Somatotropin
- Somatrem
- Somatropin

5. Any stereoisomeric form of a substance specified or described in any of paragraphs 1 to 4 of this Part of this Schedule.

6. Any salt of a substance specified or described in any of paragraphs 1 to 5 of this Part of this Schedule.

7. Any preparation or other product containing a substance or product specified or described in any of paragraphs 1 to 6 of this Part of this Schedule, not being a preparation specified in Schedule 5.

E.1.5 Schedule 5 controlled drugs

Excepted from the prohibition on importation, exportation and possession and subject to the requirements of regulations 24 and 26

1.—(1) Any preparation of one or more of the substances to which this paragraph applies, not being a preparation designed for administration by injection, when compounded with one or more other active or inert ingredients and containing a total of not more than 100 milligrams of the substance or substances (calculated as base) per dosage unit or with a total concentration of not more than 2.5% (calculated as base) in undivided preparations.

(2) The substances to which this paragraph applies are acetyldihydrocodeine, codeine, dihydrocodeine, ethylmorphine, nicocodine, nicodicodine (6-nicotinoyldihydrocodeine), norcodeine and pholcodine and their respective salts.

2. Any preparation of cocaine containing not more than 0.1% of cocaine calculated as cocaine base, being a preparation compounded with one or more other active or inert ingredients in such a way that the cocaine cannot be recovered by readily applicable means or in a yield which would constitute a risk to health.

3. Any preparation of medicinal opium or of morphine containing (in either case) not more than 0.2% of morphine calculated as anhydrous morphine base, being a preparation compounded with one or more other active or inert ingredients in such a way that the opium or, as the case may be, the morphine cannot be recovered by readily applicable means or in a yield which would constitute a risk to health.

4. Any preparation of dextropropoxyphene, being a preparation designed for oral administration, containing not more than 135 milligrams of dextropropoxyphene (calculated as base) per dosage unit or with a total concentration of not more than 2.5% (calculated as base) in undivided preparations.

5. Any preparation of difenoxin containing, per dosage unit, not more than 0.5 milligrams of difenoxin and a quantity of atropine sulphate equivalent to at least 5% of the dose of difenoxin.

6. Any preparation of diphenoxylate containing, per dosage unit, not more than 2.5 milligrams of diphenoxylate calculated as base, and a quantity of atropine sulphate equivalent to at least 1% of the dose of diphenoxylate.

7. Any preparation of propiram containing, per dosage unit, not more than 100 milligrams of propiram calculated as base and compounded with at least the same amount (by weight) of methylcellulose.

8. Any powder of ipecacuanha and opium comprising—

- 10% opium, in powder,
- 10% ipecacuanha root, in powder, well mixed with
- 80% of any other powdered ingredient containing no controlled drug.

9. Any mixture containing one or more of the preparations specified in paragraphs 1 to 8, being a mixture of which none of the other ingredients is a controlled drug.

E.2 Interrupted time series

E.2.1 Output by gender

Table E.1: Output from testing for best-fit model of interrupted time series analysis for men (all opioids)

Maximum Likelihood Estimates			
SSE	495392365	**DFE**	124
MSE	3995100	**Root MSE**	1999
SBC	2415.99783	**AIC**	2392.93541
MAE	1560.32384	**AICC**	2394.10614
MAPE	2.40060036	**HQC**	2402.30692
Log Likelihood	-1188.4677	**Transformed Regression R-Square**	0.9472

Maximum Likelihood Estimates			
Durbin-Watson	1.8623	**Total R-Square**	0.9672
		Observations	132

Table E.2: Results of interrupted time series analysis of opioid prescribing data for men

Parameter estimates				
Variable	Estimate (95% CI)	Standard Error	t Value	Approx Pr > |t|
Intercept ($ß_0$)	47169	509.7996	92.52	<<.0011
Pre-intervention trend ($ß_1$)	316.6277 (297.81 – 335.45)	9.6027	32.97	<<.0011
Change in level ($ß_2$)	573.3097	635.2972	0.90	0.3686
Post-intervention trend ($ß_3$)	-224.7378 (-273.64 - -175.83))	24.9513	-9.01	<<.0011
AR1	0.4456	0.0566	7.87	<<.0011
AR3	-0.2648	0.0634	-4.18	<<.0011
AR12	-0.3425	0.0728	-4.70	<<.0011

Table E.3: Output from testing for best-fit model of interrupted time series analysis for women (all opioids)

Maximum Likelihood Estimates			
SSE	1337137308	**DFE**	125
MSE	10697098	**Root MSE**	3271
SBC	2541.99381	**AIC**	2521.8142
MAE	2577.76903	**AICC**	2522.71742
MAPE	2.48072689	**HQC**	2530.01426
Log Likelihood	-1253.9071	**Transformed Regression R-Square**	0.9316
Durbin-Watson	1.9518	**Total R-Square**	0.9517
		Observations	132

Table E.4: Results of interrupted time series analysis of opioid prescribing data for women

Parameter estimates				
Variable	Estimate (95% CI)	Standard Error	t Value	Approx Pr > |t|
Intercept ($ß_0$)	80139	779.0447	102.87	<<.0011
Pre-intervention trend ($ß_1$)	421.1498 (392.20 – 450.45))	14.7691	28.52	<<.0011
Change in level ($ß_2$)	186.3049	1025	0.18	0.8560
Post-intervention trend ($ß_3$)	-275.5532 (-352.01 - -199.10)	39.0088	-7.06	<<.0011
AR1	0.4542	0.0579	7.85	<<.0011
AR3	-0.2920	0.0642	-4.55	<<.0011
AR12	-0.3999	0.0671	-5.96	<<.0011

E.2.2 Continuous time series analysis

The shape of the centred moving mean (CMM) graph was the same as the plot of annual prescriptions issued by the practices providing data to the SAIL databank. It demonstrated a steady monthly increase from January 2005 (Figure E.1) which appeared to be slowing and possible nearing plateau following the end of the study period (December 2015). Trendlines were fitted to the data with 'best fit' (R^2=0.9968) demonstrated by a fourth order polynomial line, although the trendlines trialled all had high coefficients of determination.

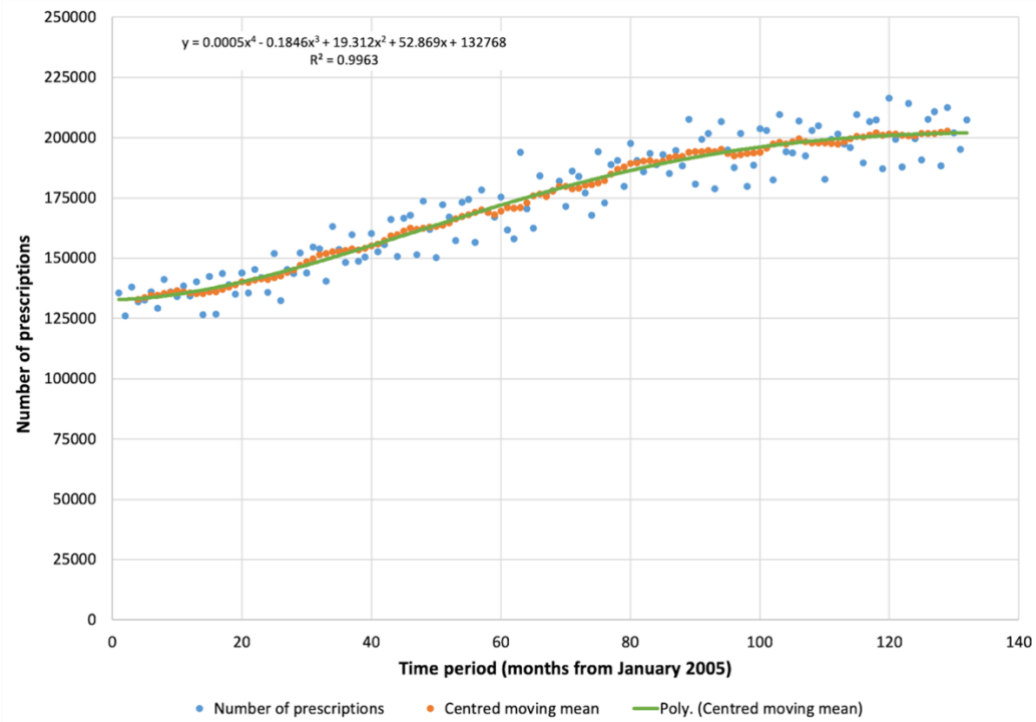


Figure E.1: Monthly trend in the number of opioid prescriptions issued from Primary Care Practices who provide data to SAIL databank. Shown with a polynomial (x4) 'best fit' trendline, R2=0.996

E.2.2.1 Weak opioids

A fourth polynomial trendline demonstrated the highest coefficient of determination for the time-series of prescription data for weak opioids over the 11-year period examined (Figure E.2). The trendline followed the expected pattern, with a slow decline in the annual number of weak opioid prescriptions issued from around month 100 (2013) to the end of the study period.

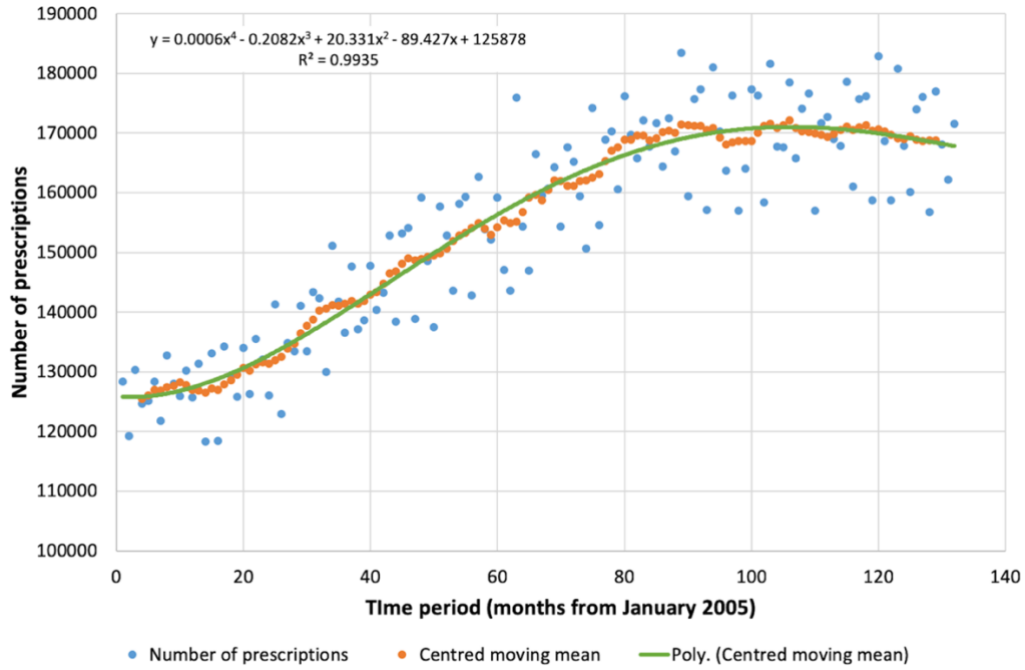


Figure E.2: Monthly trend in the number of weak opioid prescriptions issued from Primary Care Practices who provide data to SAIL databank. Shown with a polynomial 4th order 'best fit' trendline, R2=0.9935

E.2.2.2 Strong opioids

The number of strong opioid prescriptions increased steadily throughout the 11 years examined and showed no discernible pattern of seasonal variation (Figure E.3). The monthly variation was noted to mirror that seen with weak opioids, inasmuch as positive and negative effects were seen in the same months. Coefficients of determination (R^2) were good for a number of trendline models, with a fourth order polynomial trendline having the 'best fit' although the third order polynomial trendline produced a similar R^2 value.

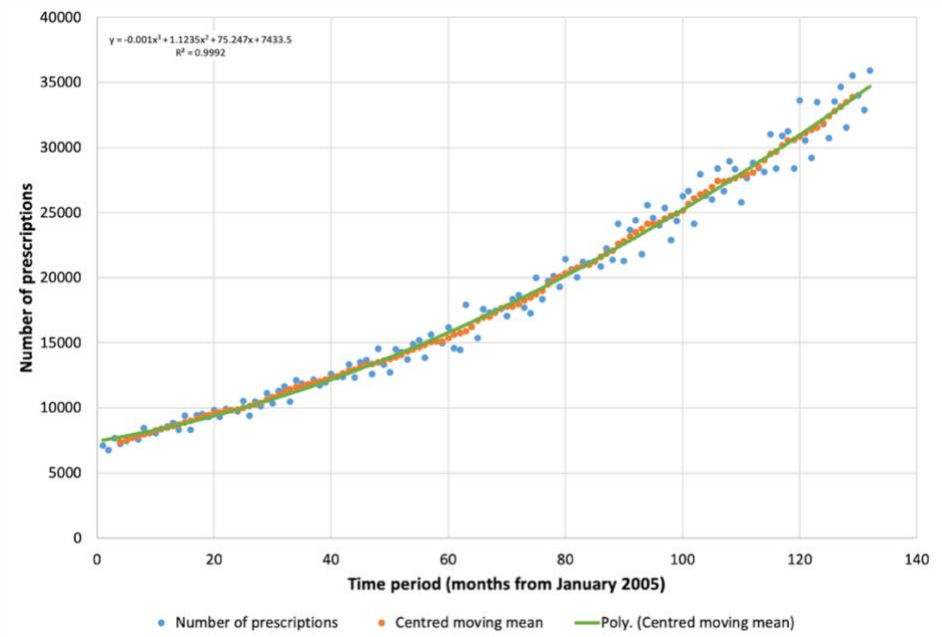


Figure E.3: Monthly trend in the number of strong opioid prescriptions issued from Primary Care Practices who provide data to SAIL databank. Shown with a polynomial trendline, R2=0.9992

E.2.2.3 Gender

Time series analysis by gender confirmed the trend in the number of prescriptions issued over the 11-year study period, seen in previous analysis). The patterns of prescribing and monthly variation were the same for the number of prescriptions issued to men and women (Figure E.4 and Figure E.5). The pattern of average seasonal effect was similar to that seen for opioids overall, with the largest variation seen, for both genders, between January and March (**Error! Reference source not found.**). The monthly variation did not appear to have any effect on the upward trend in numbers of prescriptions issued, however.

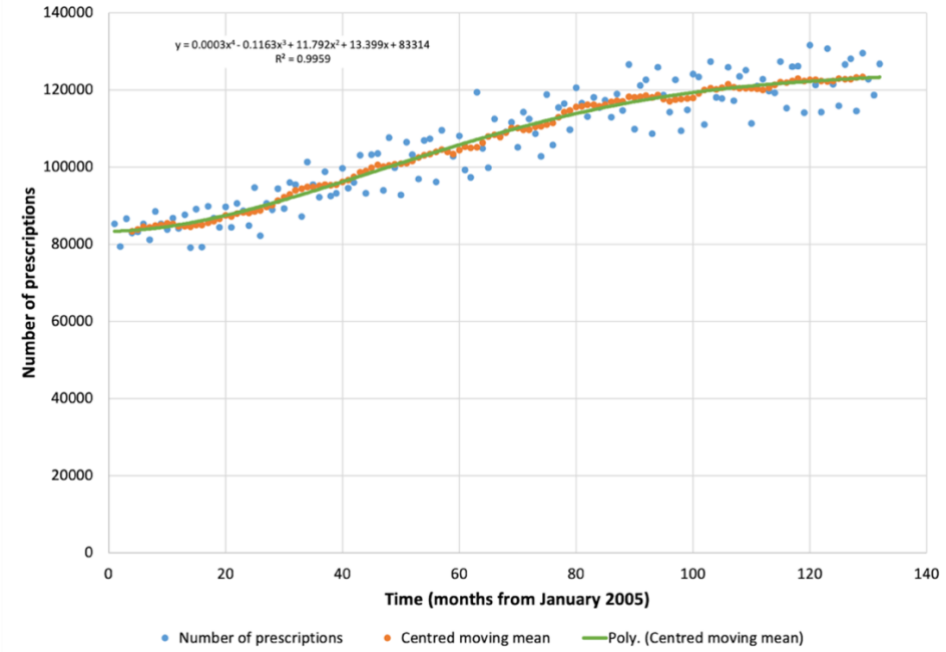


Figure E.4: Monthly trend in the number of opioid prescriptions issued to female patients from Primary Care Practices who provide data to SAIL databank. Shown with a polynomial trendline, R2=0.996

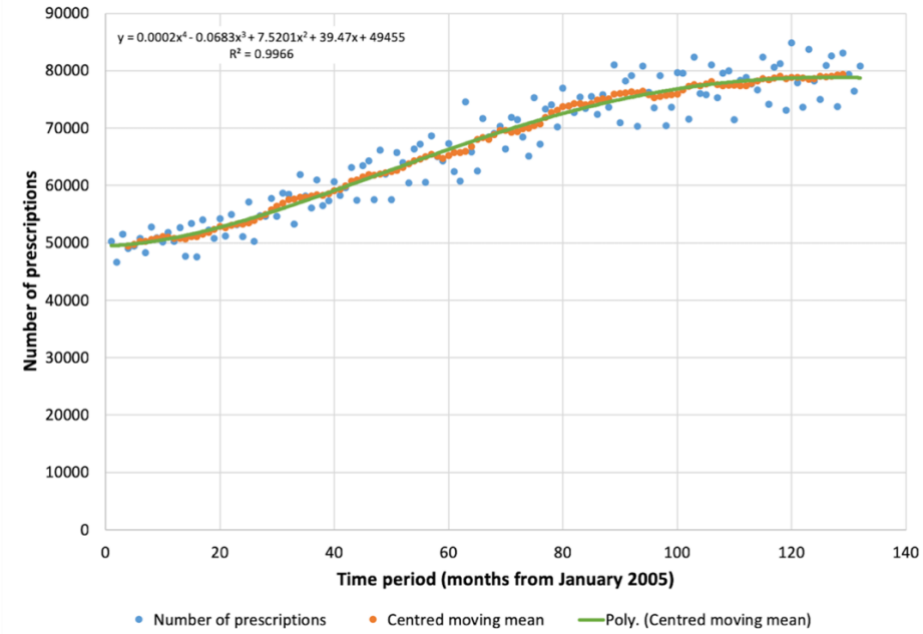


Figure E.5: Monthly trend in the number of opioid prescriptions issued to male patients from Primary Care Practices who provide data to SAIL databank. Shown with a polynomial trendline, R2=0.997

Fourth order polynomial trendlines had strong coefficients of determination (R^2) for both women and men and could therefore be seen as strong trends (Table 5 and 6).

E.2.3 Deprivation

The time series analyses for the different areas of deprivation in Wales, reflected for the most part, the trends noted in the previous analysis of population-adjusted annual prescription numbers (Figure E.6 to Figure E.10). The 4th order polynomial trendline for WIMD1 (most deprived) areas, however, was showing an upturn in 2015 (R^2 = 0.99) whereas the other 4 quintiles appeared to be plateauing or starting to reduce.

The trendline for WIMD1 areas (Figure E.6) when fitted with a 3rd order polynomial line, demonstrates the rise in numbers that is already reported (Chapter 4). The accuracy of fit of the trendlines, using 3rd or 4th order polynomial equations, were very good (R^2 > 0.990) for all areas of deprivation.

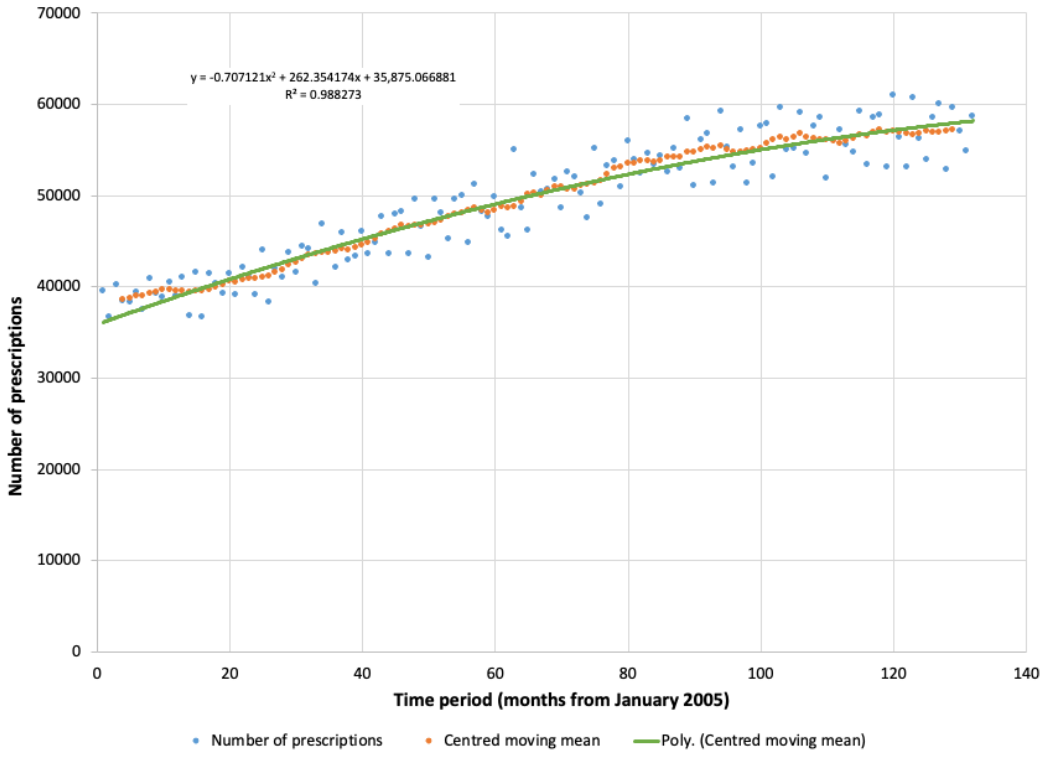


Figure E.6: Monthly trend in the number of opioid prescriptions issued to in WIMD1 (most deprived) areas. Shown with a 3rd order polynomial trendline, R2=0.996

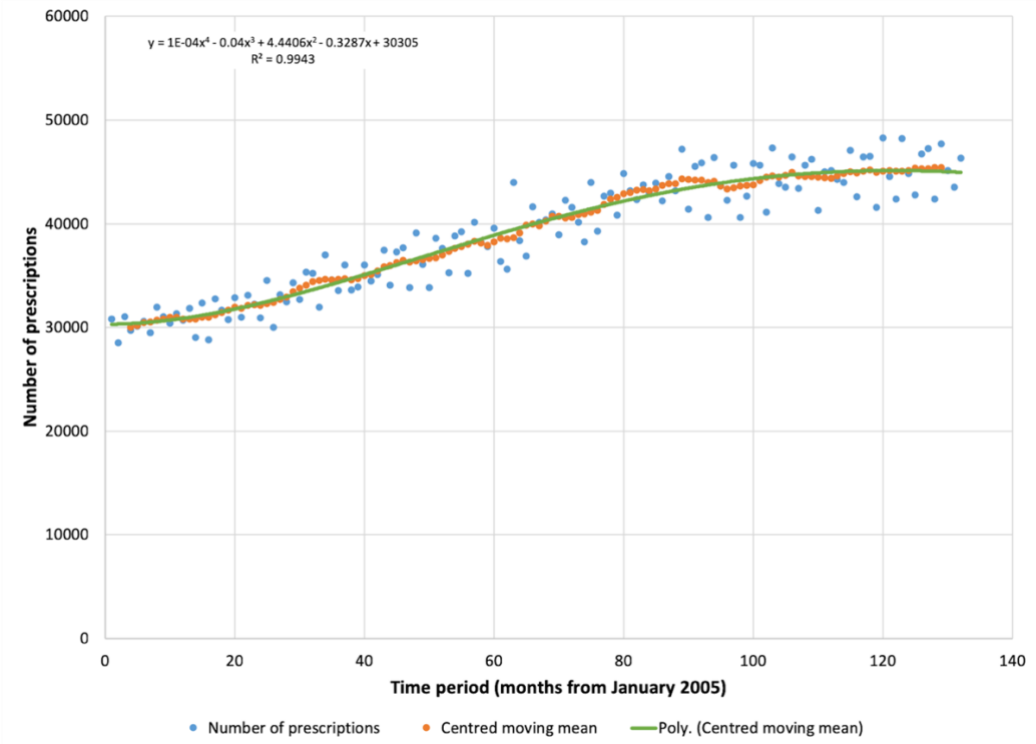


Figure E.7: Monthly trend in the number of opioid prescriptions issued to in WIMD2 areas. Shown with a 4th order polynomial trendline, R2=0.994

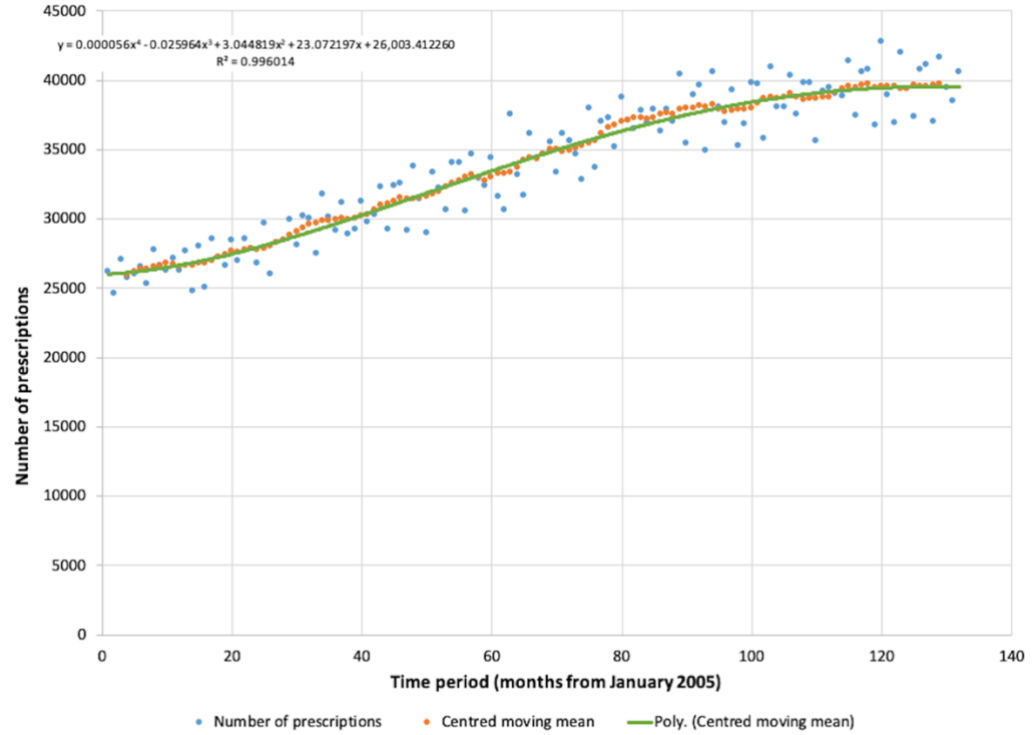


Figure E.8: Monthly trend in the number of opioid prescriptions issued to in WIMD3. Shown with a 4th order polynomial trendline, R2=0.996

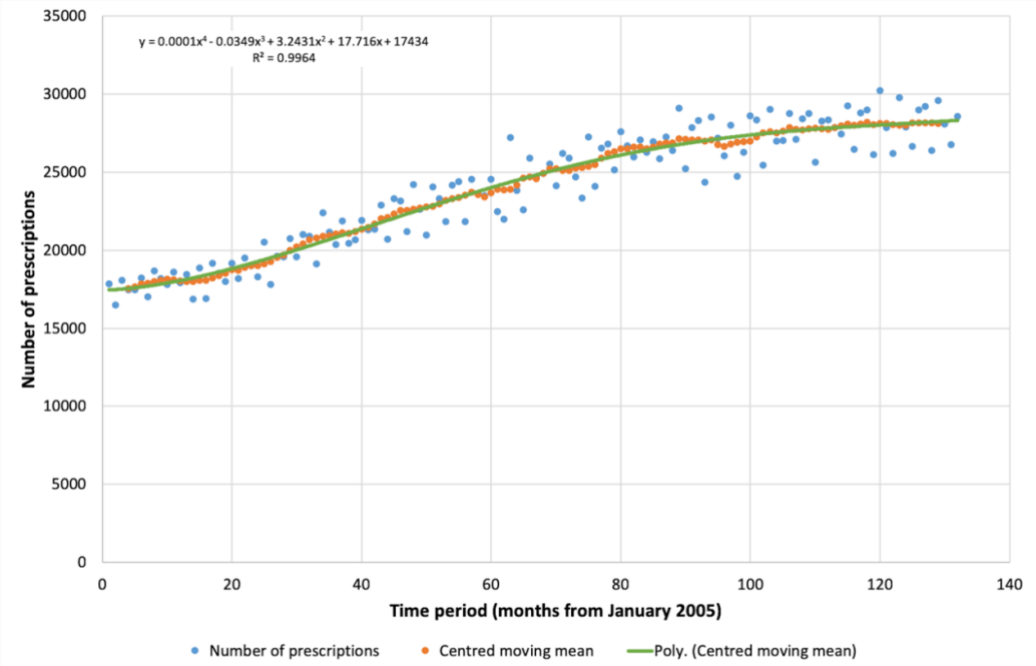


Figure E.9: Monthly trend in the number of opioid prescriptions issued to in WIMD4. Shown with a 4th order polynomial trendline, R2=0.996

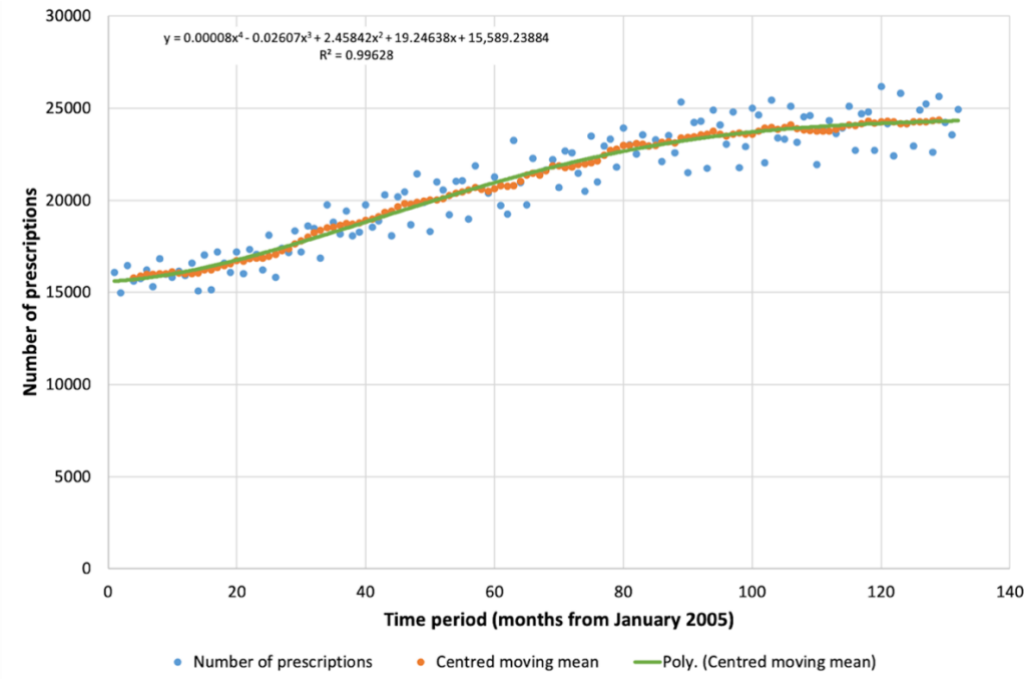


Figure E.10: Monthly trend in the number of opioid prescriptions issued to in WIMD5 (least deprived) areas. Shown with a 4th order polynomial trendline, R2=0.996

Table E.5: Example Time Series Analysis calculations

Year	Month		Frequency	moving means	centred moving mean		Month		Frequency	centred moving mean	ISE	SAV	Below/Above expectation
2005	1	1	5105				1	1	5105			5061.642	
2005	2	2	4698				2	2	4698			5092.808	
2005	3	3	5254				3	3	5254			5000.575	
2005	4	4	4977	5018	4988		4	4	4977	4988	-10.9167	5013.545	Above
2005	5	5	4976	4958	4988		5	5	4976	4988	-11.75	4984.795	Below
2005	6	6	5099	5018	4994		6	6	5099	4994	105.25	5164.273	Above
2005	7	7	4742	4970	4965		7	7	4742	4965	-222.75	4625.826	Below
2005	8	8	5059	4960	4947		8	8	5059	4947	112.5	5153.856	Above
2005	9	9	4965	4933	4886		9	9	4965	4886	79.16667	4965.235	Above
2005	10	10	4918	4839	4832		10	10	4918	4832	85.83333	4789.875	Below
2005	11	11	4816	4826	4747		11	11	4816	4747	69.25	4847.2	Above
2005	12	12	4531	4668	4650		12	12	4531	4650	-118.667	4454.217	Below
2006	1	13	4666	4632	4577		1	13	4666	4577	89.25	4622.642	Above
2006	2	14	4110	4522	4515		2	14	4110	4515	-405	4504.808	Below
2006	3	15	4749	4508	4517		3	15	4749	4517	231.5833	4495.575	Below
2006	4	16	4259	4527	4510		4	16	4259	4510	-251.167	4295.545	Below
2006	5	17	4734	4494	4548		5	17	4734	4548	185.75	4742.795	Above
2006	6	18	4642	4603	4575		6	18	4642	4575	67.08333	4707.273	Above
2006	7	19	4468	4547	4600		7	19	4468	4600	-132.083	4351.826	Below
2006	8	20	4765	4653	4657		8	20	4765	4657	107.5833	4859.856	Above
2006	9	21	4414	4662	4657		9	21	4414	4657	-242.833	4414.235	Below
2006	10	22	4896	4652	4700		10	22	4896	4700	196.25	4767.875	Above
2006	11	23	4785	4748	4726		11	23	4785	4726	58.66667	4816.2	Above
2006	12	24	4584	4705	4746		12	24	4584	4746	-162.333	4507.217	Below
2007	1	25	5041	4788	4783		1	25	5041	4783	258.25	4997.642	Above

2007	2	26	4511	4778	4802		2	26	4511	4802	-290.667	4905.808	Above
2007	3	27	4908	4825	4839		3	27	4908	4839	68.58333	4654.575	Below
2007	4	28	4839	4854	4867		4	28	4839	4867	-27.6667	4875.545	Above
2007	5	29	5069	4880	4941		5	29	5069	4941	128.1667	5077.795	Above
2007	6	30	4753	5002	4983		6	30	4753	4983	-230.417	4818.273	Below
2007	7	31	5199	4965	5018		7	31	5199	5018	180.8333	5082.826	Above
2007	8	32	5243	5071	5082		8	32	5243	5082	161.5	5337.856	Above
2007	9	33	4687	5092	5104		9	33	4687	5104	-417.083	4687.235	Below
2007	10	34	5477	5117	5129		10	34	5477	5129	348.1667	5348.875	Above
2007	11	35	5191	5141	5118		11	35	5191	5118	72.66667	5222.2	Above
2007	12	36	4902	5096	5135		12	36	4902	5135	-232.5	4825.217	Below
2008	1	37	5347	5174	5167		1	37	5347	5167	179.5833	5303.642	Above
2008	2	38	4969	5161	5155		2	38	4969	5155	-186.167	5363.808	Above
2008	3	39	5155	5149	5170		3	39	5155	5170	-15.3333	4901.575	Below
2008	4	40	5404	5192	5217		4	40	5404	5217	187.0833	5440.545	Above
2008	5	41	5117	5242	5251		5	41	5117	5251	-134.25	5125.795	Below
2008	6	42	5158	5260	5294		6	42	5158	5294	-136.25	5223.273	Below
2008	7	43	5650	5328	5350		7	43	5650	5350	299.8333	5533.826	Above
2008	8	44	5078	5372	5364		8	44	5078	5364	-286.417	5172.856	Below
2008	9	45	5562	5357	5402		9	45	5562	5402	160	5562.235	Above
2008	10	46	5668	5447	5421		10	46	5668	5421	246.6667	5539.875	Above
2008	11	47	5024	5395	5385		11	47	5024	5385	-361	5055.2	Below
2008	12	48	5702	5375	5389		12	48	5702	5389	313.1667	5625.217	Above
2009	1	49	5338	5403	5387		1	49	5338	5387	-48.9167	5294.642	Below
2009	2	50	4954	5371	5384		2	50	4954	5384	-429.75	5348.808	Below
2009	3	51	5732	5397	5388		3	51	5732	5388	344.4167	5478.575	Above
2009	4	52	5475	5379	5414		4	52	5475	5414	60.83333	5511.545	Above
2009	5	53	5179	5450	5468		5	53	5179	5468	-289.417	5187.795	Below

2009	6	54	5593	5487	5498		6	54	5593	5498	95	5658.273	Above
2009	7	55	5766	5509	5511		7	55	5766	5511	254.6667	5649.826	Above
2009	8	56	5177	5514	5535		8	56	5177	5535	-357.833	5271.856	Below
2009	9	57	5864	5556	5565		9	57	5864	5565	298.8333	5864.235	Above
2009	10	58	5503	5574	5532		10	58	5503	5532	-28.75	5374.875	Below
2009	11	59	5433	5489	5490		11	59	5433	5490	-57	5464.2	Below
2009	12	60	5703	5491	5576		12	60	5703	5576	126.5833	5626.217	Above
2010	1	61	5255	5662	5671		1	61	5255	5671	-415.667	5211.642	Below
2010	2	62	5187	5679	5668		2	62	5187	5668	-480.667	5581.808	Below
2010	3	63	6891	5656	5676		3	63	6891	5676	1214.75	6637.575	Above
2010	4	64	5607	5697	5738		4	64	5607	5738	-131.167	5643.545	Below
2010	5	65	5293	5780	5842		5	65	5293	5842	-548.583	5301.795	Below
2010	6	66	5946	5903	5833		6	66	5946	5833	113.5	6011.273	Above
2010	7	67	5755	5762	5777		7	67	5755	5777	-21.8333	5638.826	Below
2010	8	68	5928	5792	5867		8	68	5928	5867	60.58333	6022.856	Above
2010	9	69	6041	5943	5966		9	69	6041	5966	74.91667	6041.235	Above
2010	10	70	5789	5989	6004		10	70	5789	6004	-214.75	5660.875	Below
2010	11	71	6198	6018	5985		11	71	6198	5985	212.9167	6229.2	Above
2010	12	72	6225	5952	5981		12	72	6225	5981	243.5833	6148.217	Above
2011	1	73	5928	6011	6006		1	73	5928	6006	-78.1667	5884.642	Below
2011	2	74	5531	6002	6007		2	74	5531	6007	-475.5	5925.808	Below
2011	3	75	6394	6012	6019		3	75	6394	6019	374.6667	6140.575	Above
2011	4	76	5733	6027	6029		4	76	5733	6029	-295.5	5769.545	Below
2011	5	77	6258	6030	6116		5	77	6258	6116	142.3333	6266.795	Above
2011	6	78	6319	6202	6208		6	78	6319	6208	110.9167	6384.273	Above
2011	7	79	5944	6215	6249		7	79	5944	6249	-305.417	5827.826	Below
2011	8	80	6561	6284	6317		8	80	6561	6317	244.25	6655.856	Above
2011	9	81	6473	6349	6348		9	81	6473	6348	125.0833	6473.235	Above

2011	10	82	6150	6347	6395		10	82	6150	6395	-244.667	6021.875	Below
2011	11	83	6649	6443	6408		11	83	6649	6408	241.3333	6680.2	Above
2011	12	84	6302	6373	6376		12	84	6302	6376	-74.4167	6225.217	Below
2012	1	85	6522	6380	6389		1	85	6522	6389	132.5833	6478.642	Above
2012	2	86	6139	6399	6440		2	86	6139	6440	-301.25	6533.808	Above
2012	3	87	6520	6482	6475		3	87	6520	6475	45.08333	6266.575	Below
2012	4	88	6259	6468	6495		4	88	6259	6495	-235.917	6295.545	Below
2012	5	89	7150	6522	6582		5	89	7150	6582	568.4167	7158.795	Above
2012	6	90	6217	6641	6595		6	90	6217	6595	-378.417	6282.273	Below
2012	7	91	6847	6550	6609		7	91	6847	6609	238.25	6730.826	Above
2012	8	92	6854	6668	6622		8	92	6854	6622	232.3333	6948.856	Above
2012	9	93	5971	6576	6587		9	93	5971	6587	-615.75	5971.235	Below
2012	10	94	6968	6598	6589		10	94	6968	6589	378.9167	6839.875	Above
2012	11	95	6596	6580	6522		11	95	6596	6522	73.58333	6627.2	Above
2012	12	96	6352	6465	6487		12	96	6352	6487	-135.417	6275.217	Below
2013	1	97	6740	6510	6502		1	97	6740	6502	238.0833	6696.642	Above
2013	2	98	6161	6494	6511		2	98	6161	6511	-350.25	6555.808	Above
2013	3	99	6244	6529	6516		3	99	6244	6516	-272.083	5990.575	Below
2013	4	100	6869	6503	6539		4	100	6869	6539	329.5833	6905.545	Above
2013	5	101	6807	6576	6624		5	101	6807	6624	183.1667	6815.795	Above
2013	6	102	6199	6672	6710		6	102	6199	6710	-510.583	6264.273	Below
2013	7	103	7173	6747	6778		7	103	7173	6778	395.5	7056.826	Above
2013	8	104	6741	6808	6803		8	104	6741	6803	-61.9167	6835.856	Above
2013	9	105	6693	6798	6876		9	105	6693	6876	-182.75	6693.235	Below
2013	10	106	7235	6954	6948		10	106	7235	6948	287.5	7106.875	Above
2013	11	107	6746	6941	6909		11	107	6746	6909	-163.083	6777.2	Below
2013	12	108	7134	6877	6902		12	108	7134	6902	232	7057.217	Above
2014	1	109	7099	6927	6920		1	109	7099	6920	179.25	7055.642	Above

2014	2	110	6354	6912	6942		2	110	6354	6942	-587.667	6748.808	Below
2014	3	111	6995	6971	6961		3	111	6995	6961	34.25	6741.575	Below
2014	4	112	7146	6951	6985		4	112	7146	6985	160.75	7182.545	Above
2014	5	113	7098	7020	7057		5	113	7098	7057	40.91667	7106.795	Above
2014	6	114	7011	7094	7142		6	114	7011	7142	-131.417	7076.273	Below
2014	7	115	7516	7191	7230		7	115	7516	7230	286	7399.826	Above
2014	8	116	6799	7269	7255		8	116	6799	7255	-456.417	6893.856	Below
2014	9	117	7574	7242	7325		9	117	7574	7325	249.4167	7574.235	Above
2014	10	118	7618	7408	7392		10	118	7618	7392	226.0833	7489.875	Above
2014	11	119	6931	7376	7390		11	119	6931	7390	-459.333	6962.2	Below
2014	12	120	8008	7405	7432		12	120	8008	7432	575.8333	7931.217	Above
2015	1	121	7327	7460	7428		1	121	7327	7428	-100.667	7283.642	Below
2015	2	122	6969	7396	7410		2	122	6969	7410	-441.167	7363.808	Below
2015	3	123	7906	7425	7398		3	123	7906	7398	508.3333	7652.575	Above
2015	4	124	7232	7371	7420		4	124	7232	7420	-187.917	7268.545	Below
2015	5	125	7107	7469	7469		5	125	7107	7469	-361.5	7115.795	Below
2015	6	126	7682	7468	7505		6	126	7682	7505	177.3333	7747.273	Above
2015	7	127	7920	7542	7615		7	127	7920	7615	304.9167	7803.826	Above
2015	8	128	6959	7689	7759		8	128	6959	7759	-799.583	7053.856	Below
2015	9	129	8350	7829	7882		9	129	8350	7882	468.4167	8350.235	Above
2015	10	130	8113	7935			10	130	8113			7984.875	Above
2015	11	131	7948				11	131	7948			7979.2	Above
2015	12	132	8317				12	132	8317			8240.217	Above
2016	1	133	27287										
2016	2	134											

Average seasonal effects	
January	43.35833
February	-394.808
March	253.425
April	-36.5455
May	-8.79545
June	-65.2727
July	116.1742
August	-94.8561
September	-0.23485
October	128.125
November	-31.2
December	76.78333

*When the seasonal effect is positive this means that this month you would expect more patients than another month.

To get a prediction, substitute the time value into the equation on the graph and add the seasonal effect

E.g.,
Predicted value for January 2019 would be:

	y = 629.1x	Seasonal effect =
x = 169	+ 131026	2349.183

Prediction for Jan 2019
237387.3

Predicted value for February 2019 would be:

	y = 629.1x	Seasonal effect = -11018.1
x = 170	+ 131026	

Prediction for Feb 2019
237578.2

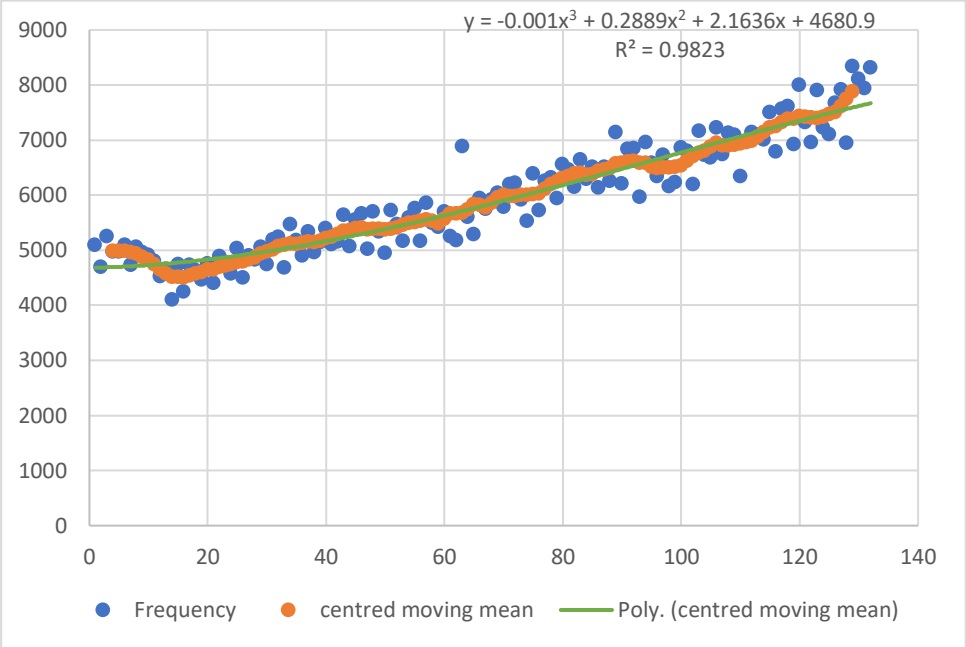


Figure E.11: Example of calculation for seasonal variation (Top) and example TSA plot from which the seasonal variations were calculated

E.3 Predictions

E.3.1 Predictions for weak opioid prescribing

The predicted trends in the number of weak opioid prescriptions using the equations generated from the trendline analyses, were very similar to those seen for all opioid prescribing (Figure E.12). Two predictions were for prescribing to continue to prescribe, albeit following the quadratic polynomial prediction, there

would be an initial plateauing prior to a further increase. As with the total opioid predictions, the 3rd order polynomial equation suggests there could be a dramatic reduction in the number of weak opioid prescriptions issued. Whilst that trendline had a high R^2 value (Table E.6) at prediction hints weak opioid prescribing could reduce to zero by the end of 2022.

Table E.6: Comparison of predicted trends in weak opioid prescribing using trendline analysis

	Polynomial			Linear
	x^2	x^3	x^4	
R^2	0.9767	0.9916	0.9935	0.9054
Predicted values				
January 2018	169996	142712	174157	194848
January 2020	162264	98508	187502	204921

The linear trendline had the lowest coefficient of determination of any of the lines (Table 3) and was suggestive of a continued increase in the annual number of weak opioid prescriptions issued.

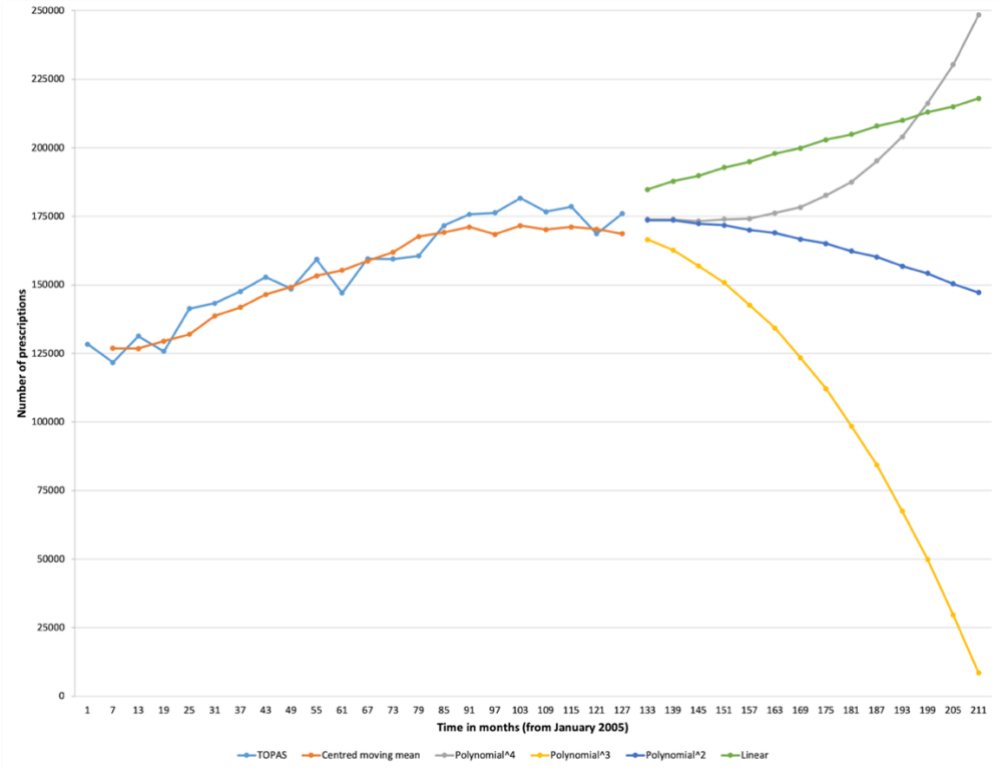


Figure E.12: Predicted trends in the number of weak opioid prescriptions issued using different time-series trendline analysis

E.3.2 Predictions for strong opioid prescribing

Three of the four predictions for strong opioid prescribing anticipated continued increases in the number of prescriptions issued in the time following the end of the study period (Figure E.13). The trendline of 'best fit' (4th order polynomial), predicted a further increase in strong opioid prescriptions being issued until mid 2019 before downturn in the number of prescriptions.

Table E.7: Comparison of predicted trends in strong opioid prescribing using trendline analysis

	Exponential	Polynomial		Linear
		x^3	x^4	
R^2	0.9973	0.9992	0.9994	0.9788
Predicted values				
January 2018	49388	43072	40999	37295
January 2020	65871	51931	42972	42320

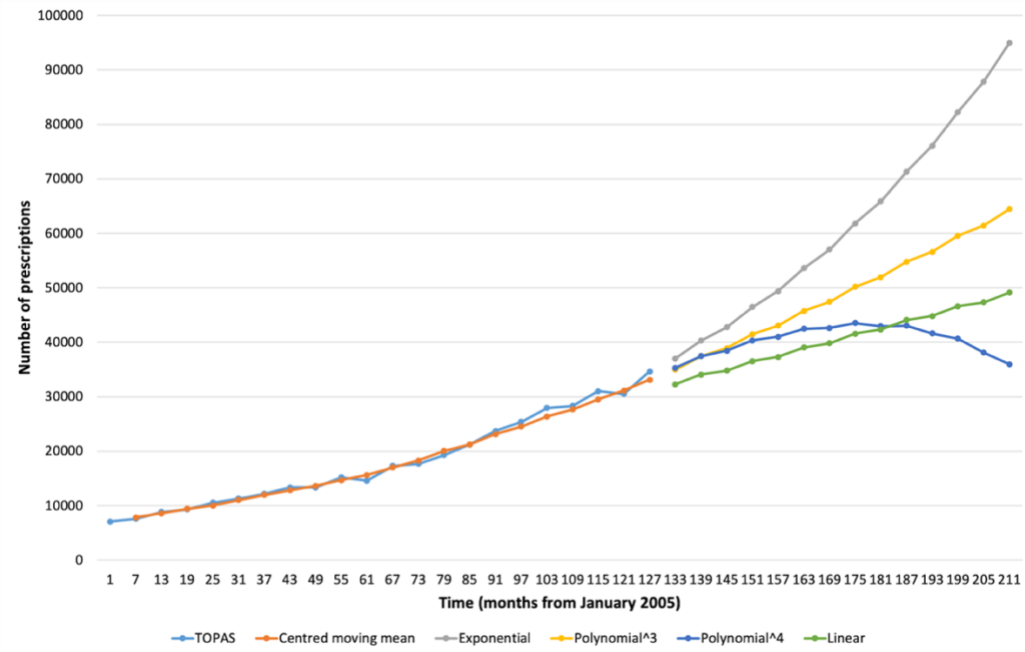


Figure E.13: Predicted trends in the number of strong opioid prescriptions issued using different time-series trendline analysis

E.3.3 Predictions by gender

In the female group, the trendline predictions (Figure E.14) mooted the annual number of opioid prescriptions could increase in 2 scenarios and decrease in another 2, assuming no changes were made to any factors which could influence prescribing.

The number of prescriptions for men appeared to increase in 3 of 4 predictions (Figure E.15), the difference being how quickly change could occur if nothing was done to intervene.

Table E.8: Comparison of predicted trends in opioid prescribing for female patients using trendline analysis

	Polynomial			Linear
	x^2	x^3	x^4	
R^2	0.988	0.995	0.996	0.970
Predicted values	129517	114521	109677	140026
January 2018	130606	95577	105808	148644
January 2020				

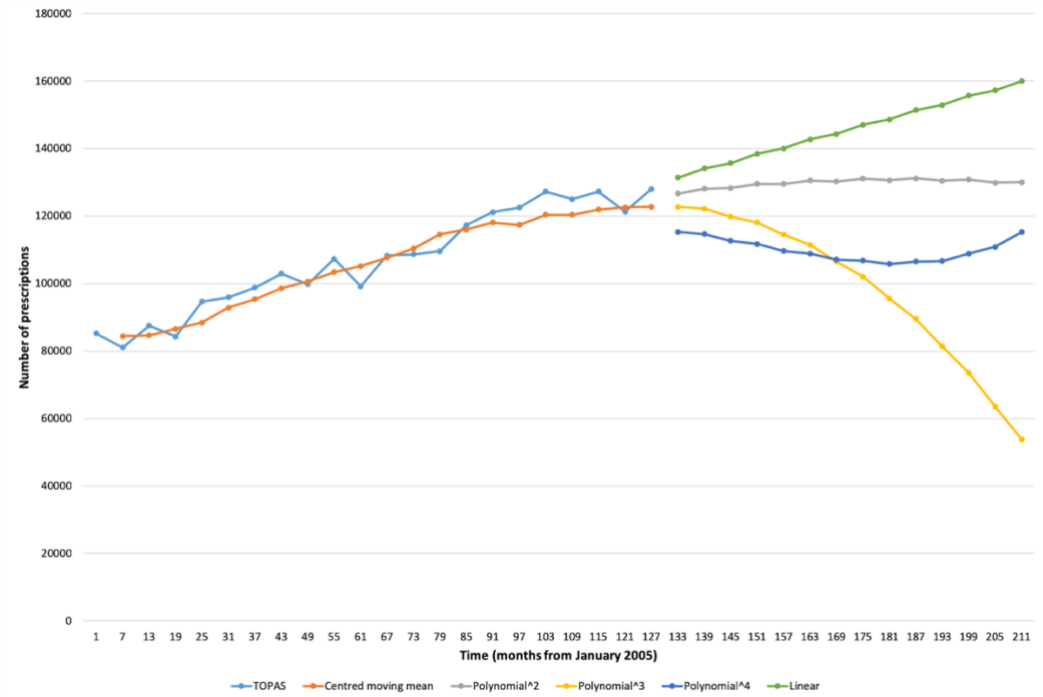


Figure E.14: Predicted trends in the number of opioid prescriptions issued to women using different time-series trendline analysis

Table E.9: Comparison of predicted trends in opioid prescribing for male patients using trendline analysis

	Polynomial			Linear
	x^2	x^3	x^4	
R^2	0.988	0.996	0.997	0.969
Predicted values January 2018	84150	71263	99170	92118
January 2020	84921	54863	113574	98598

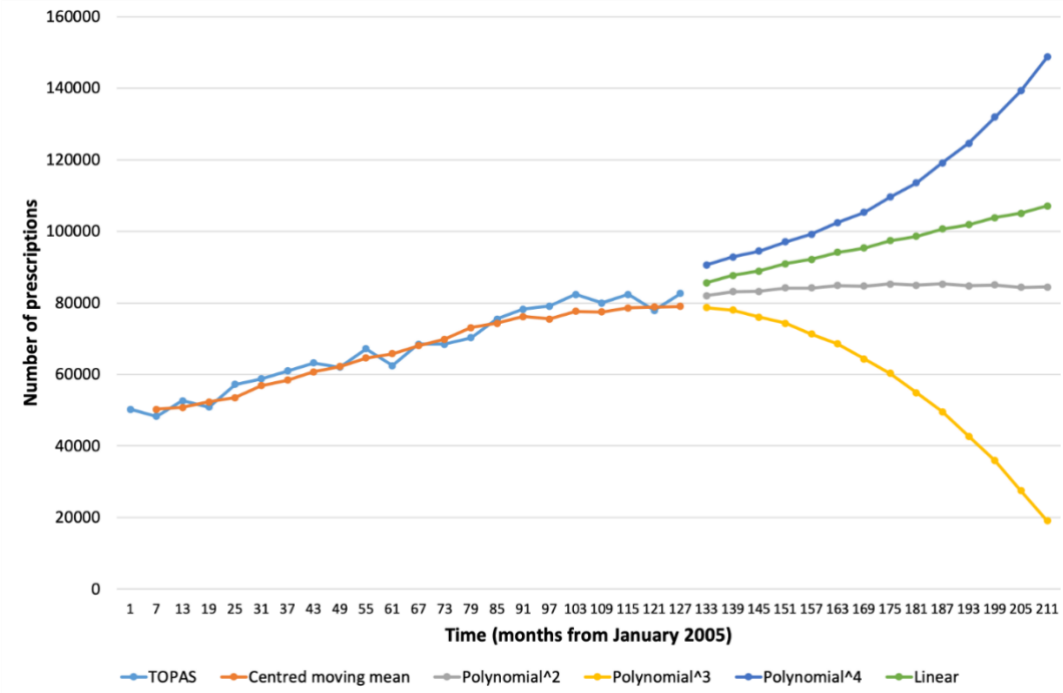


Figure E.15: Predicted trends in the number of opioid prescriptions issued to men using different time-series trendline analysis

E.3.4 Predictions by deprivation

Continuation of the 4th order polynomial trendlines for each area of deprivation appeared to predict, that should those trends continue, by 2020 (Table E.10) the difference in the number of opioid prescriptions issued in each area of deprivation throughout Wales would be smaller than in 2015 (Figure E.16).

Table E.10: Comparison of predicted trends in opioid prescribing for Health Boards using trendline analysis

	Welsh Index of Multiple Deprivation (WIMD)				
	1	**2**	**3**	**4**	**5**
Polynomial R^2 (x^2)	0.988	0.983	0.988	0.990	0.990
Predicted values					
January 2018	60413	47704	42433	29201	25126
January 2020	60974	47856	43218	28872	24798
Polynomial R^2 (x^4)	0.996	0.994	0.996	0.996	0.996
Predicted values					
January 2018	46970	45581	40668	26135	27217
January 2020	45307	45793	40315	27550	31178

Based on those predictions, there would be a reduction in the number of prescriptions issued in the areas with the greatest deprivation (WIMD1). The change seen from 2016, based on the polynomial prediction (R^2 = 0.99) but would undergo an upturn in around 2020. The WIMD3 areas were predicted to maintain prescribing at consistent levels after 2015 (R^2 = 0.996), whereas the remaining three areas (WIMD2, WIMD4 and WIMD5) were predicted to have an increase in opioid prescription numbers, most notably in the least deprived areas (Table E.10).

The result of the predicted changes in prescribing from 4th order polynomial equations, is that over the time period predicted, the difference in the number of prescriptions issued in each of the deprivation areas, looked to reduce. If borne out, that would lead to similar numbers of opioid prescriptions being issued in all five areas of deprivation across Wales.

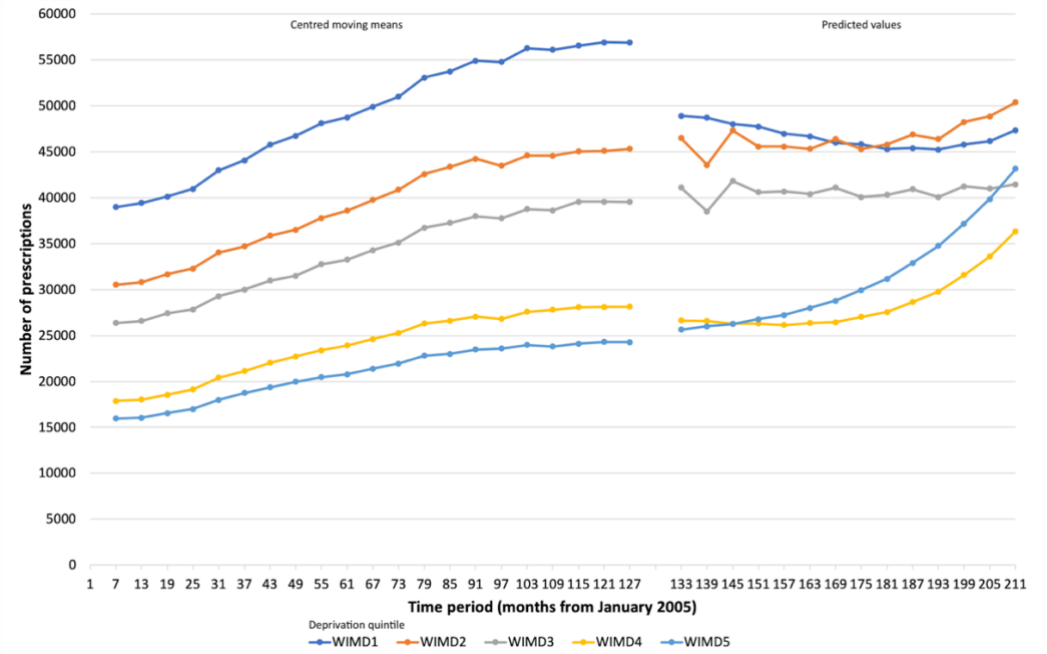


Figure E.16: Predicted trends in the number of opioid prescriptions issued to people in the different areas of deprivation (WIMD2011) (4th order polynomial prediction)
WIMD1 = most deprived, WIMD5 = least deprived

The second order polynomial predictions appeared to follow on from the trends noted in the study period. Although the predictions seem to show a continued increase in the number of prescriptions issued in each area overall; the trendlines show a slowdown in the rate of increase.

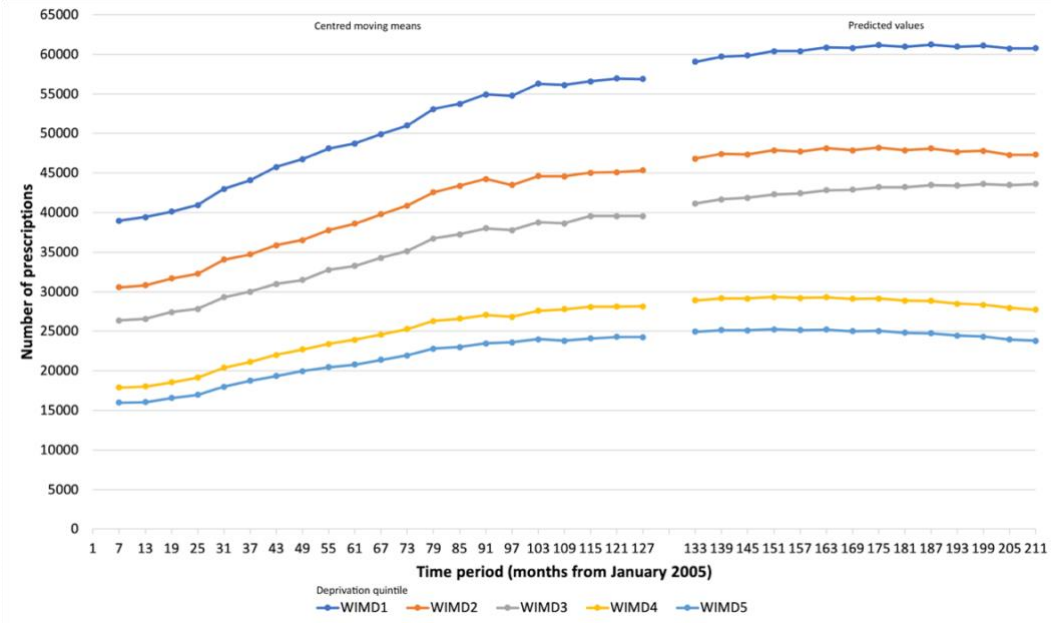


Figure E.17: Predicted trends in the number of opioid prescriptions issued to people in the different areas of deprivation (WIMD2011) (2nd order polynomial prediction)
WIMD1 = most deprived, WIMD5 = least deprived

In the least deprived areas (WIMD4 and WIMD5), there were predicted reductions towards the end of the period (Figure E.17). The predicted change from the second order polynomial trendlines demonstrate a further widening in

the difference between prescribing of opioids in the most and least deprived areas.

E.3.5 Prescribing by Health Board

Time series analyses for each Health Board (HB) was conducted using the original data (not population adjusted) from the SAIL datasets. However, the 4th order polynomial trendlines for each HB were the same as those seen for the population adjusted prescribing trend graphs (Figure E.18 to Figure E.24).

Based on the trendlines, two Health Boards (ABMUHB R^2 = 0.99, Figure E.18 and HDUHB R^2 = 0.99, Figure E.19) appeared to be demonstrating a continued, albeit slowing increase in the number of prescriptions issued. The other five HBs appeared to be showing a turnaround in prescription numbers towards the end of the study period in 2015 (Figure E.20 to Figure E.24).

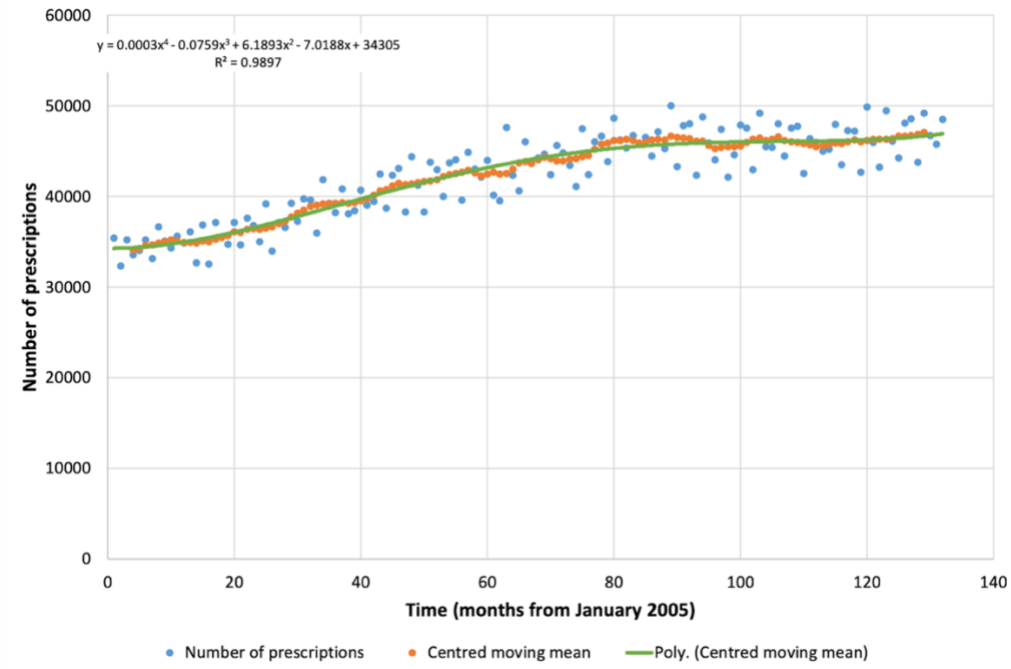


Figure E.18: Monthly trend in the number of opioid prescriptions issued to in Abertawe Bro Morgannwg University Health Board. Shown with a 4th order polynomial trendline, R2=0.990

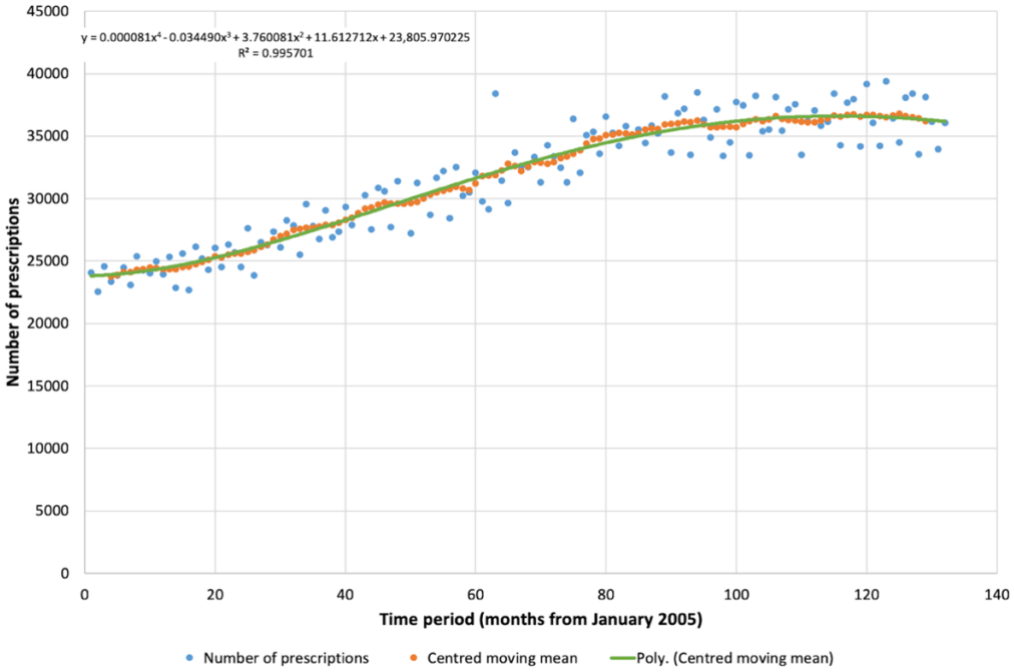


Figure E.19: Monthly trend in the number of opioid prescriptions issued to in Aneurin Bevan University Health Board. Shown with a 4th order polynomial trendline, R2=0.996

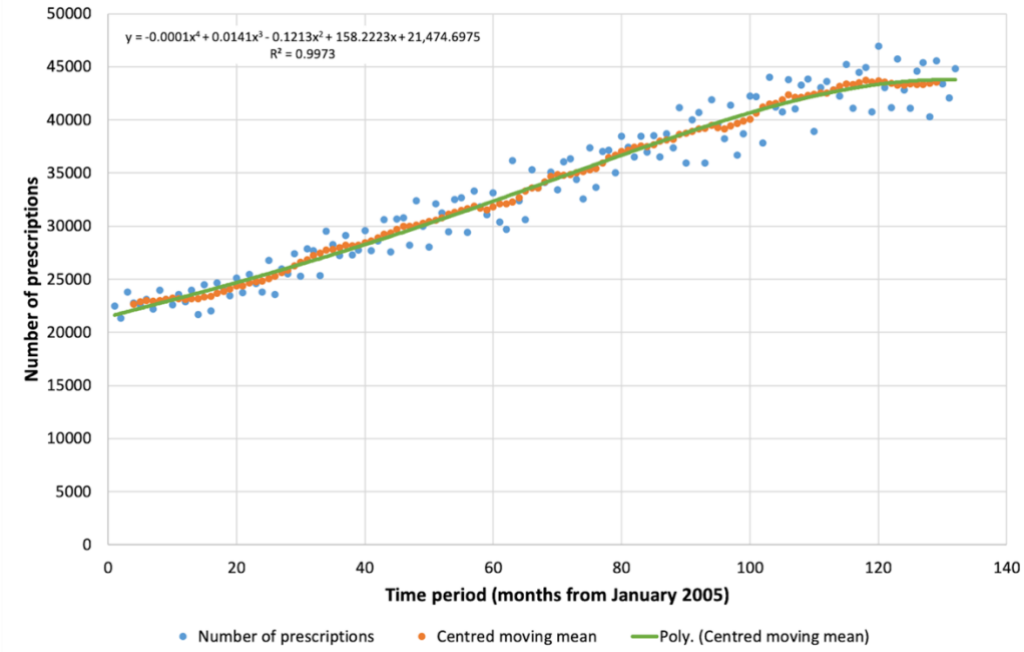


Figure E.20: Monthly trend in the number of opioid prescriptions issued to in Betsi Cadwaladr University Health Board. Shown with a 4th order polynomial trendline, R2=0.997

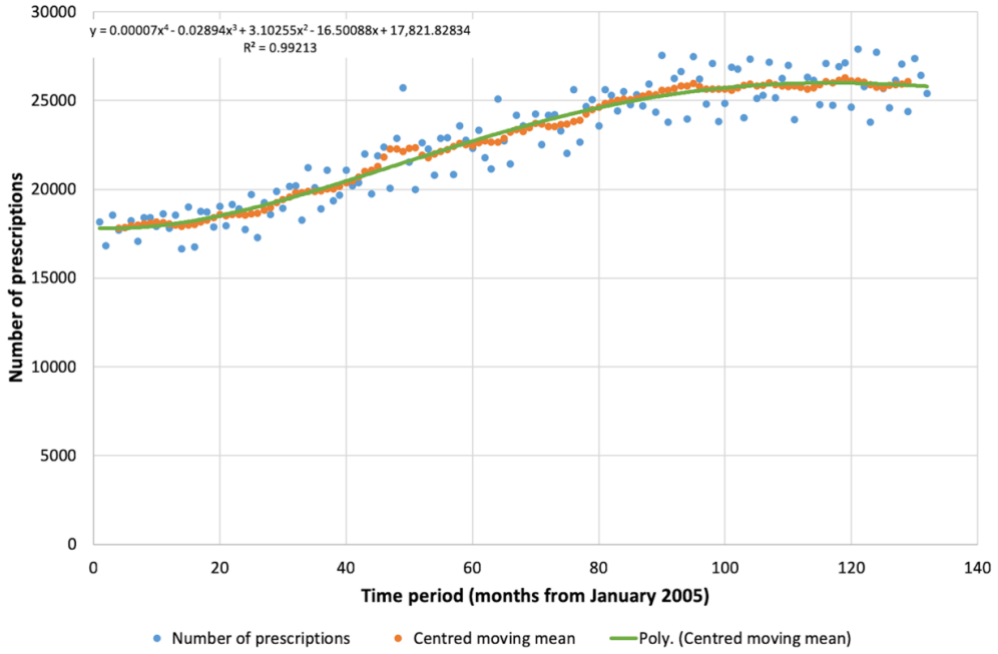


Figure E.21: Monthly trend in the number of opioid prescriptions issued to in Cardiff and Vale University Health Board. Shown with a 4th order polynomial trendline, R2=0.992

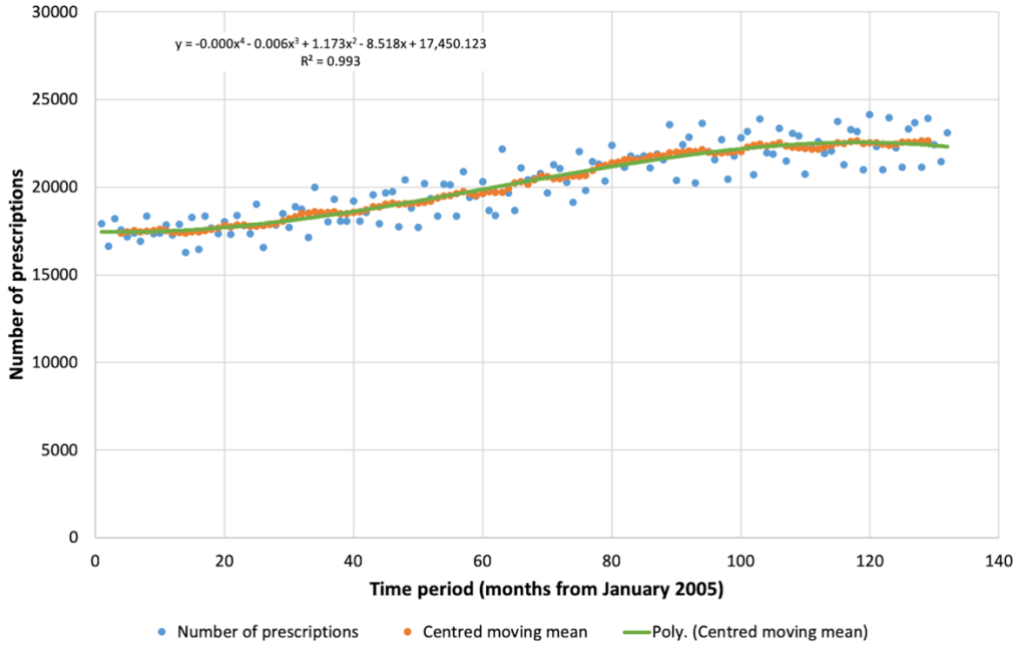


Figure E.22: Monthly trend in the number of opioid prescriptions issued to in Cwm Taf University Health Board. Shown with a 4th order polynomial trendline, R2=0.993

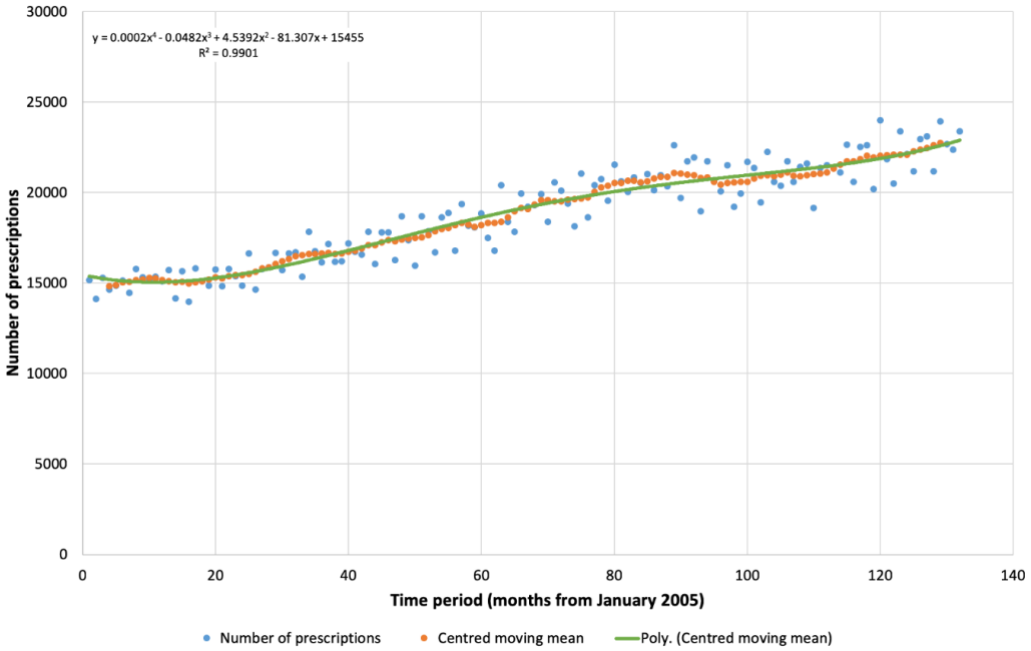


Figure E.23: Monthly trend in the number of opioid prescriptions issued to in Hywel Dda University Health Board. Shown with a 4th order polynomial trendline, R2=0.990

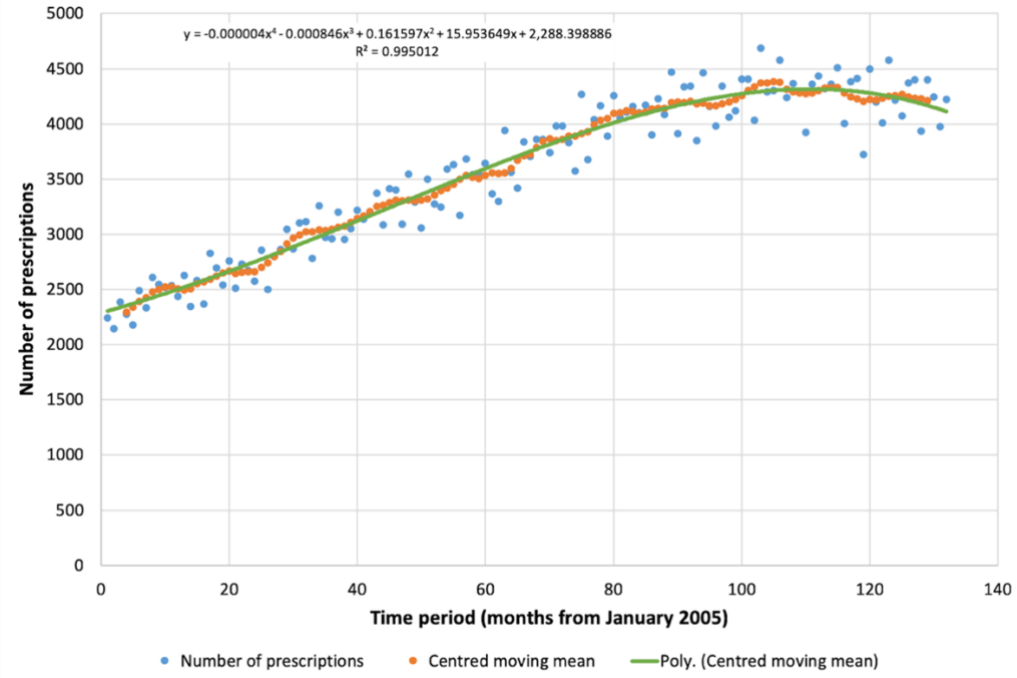


Figure E.24: Monthly trend in the number of opioid prescriptions issued to in Powys Teaching Health Board. Shown with a 4th order polynomial trendline, R2=0.995

Average seasonal effects were similar in pattern as were seen with the total opioid prescribing trends (Figure E.25). The exception was CVUHB (R^2 = 0.992) which had a different pattern in the average seasonal effect to the other HBs although there was still no clear seasonal trend in any Health Board.

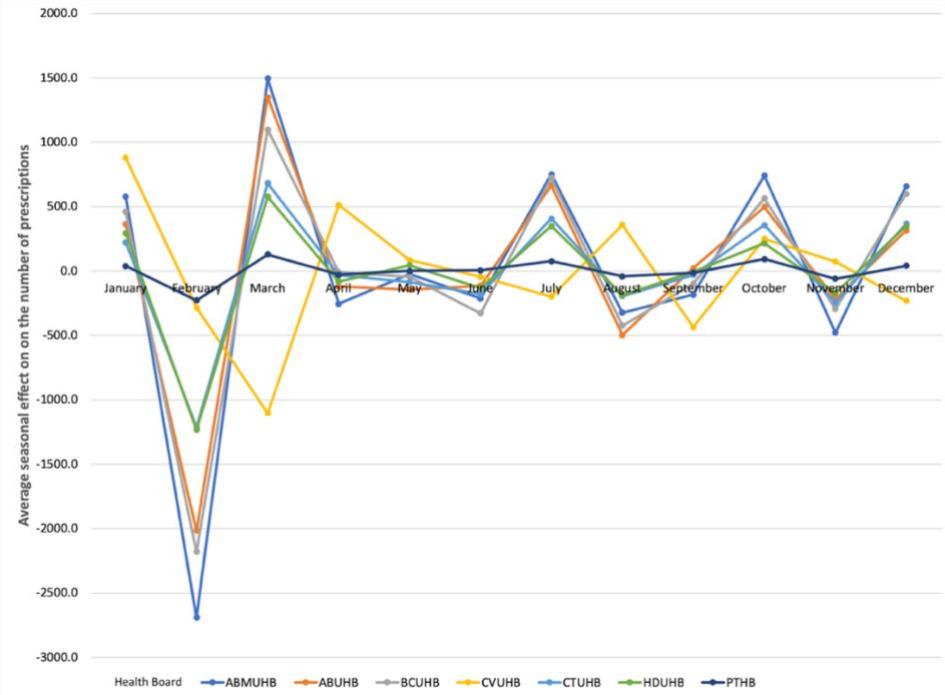


Figure E.25: Graphical depiction of average seasonal variation in the number of opioid prescriptions issued by Health Board, from time series analysis
ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwallader University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

E.4 Predictions for Health Board prescribing

The polynomial trendlines were continued via calculation to predict possible changes in number of prescriptions that could be issued in each Health Board following the end of the study period in 2015 (Table E.11 and Figure E.26).Fourth order polynomial equations predicted dramatic increases in the number of prescriptions issued after 2015 in ABMUHB and HDUHB (Figure E.26). The changes appeared remote from the end of the trendlines in 2015 but due to the nature of 4th order polynomial trendlines sudden changes in either direction is possible. Interestingly however, the 5 other Health Boards were predicted to demonstrate reductions in prescriptions numbers issued.

Table E.11: Comparison of predicted trends in opioid prescribing for Health Boards using trendline analysis

	Health Board						
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**	**PTHB**
Polynomial R^2 (x^2)	0.981	0.983	0.993	0.980	0.974	0.980	0.983
Predicted values							
January 2018	45488	38020	50277	27676	24285	23950	4360
January 2020	42961	37479	54066	27405	25014	24784	4180
Polynomial R^2 (x^4)	0.990	0.996	0.997	0.992	0.993	0.990	0.995
Predicted values							
January 2018	74887	30772	37593	23120	20759	49856	3110
January 2020	108297	27673	22880	20879	16467	78584	1199

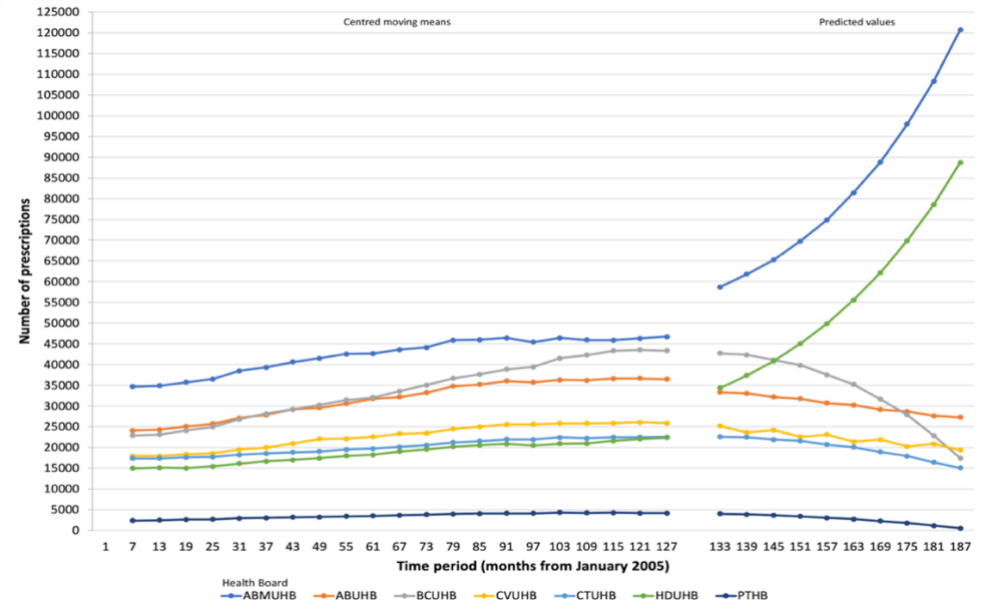


Figure E.26: Predicted trends in the number of opioid prescriptions issued to people in the 7 Health Boards (4th order polynomial prediction)

ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Second order polynomial equations predicted future trends appeared to follow the previous patterns of prescribing more realistically (Figure E.27). Using those predictions, BCUHB could have the largest continued increase in the number of opioid prescriptions issued monthly after the end of the TOPAS study period in 2015. ABMUHB prediction was of a reduction in the number of prescriptions being issued after 2015 (Figure E.27). The other HBs were predicted to have much slower increases or plateau in prescription numbers after 2015 (Figure E.27).

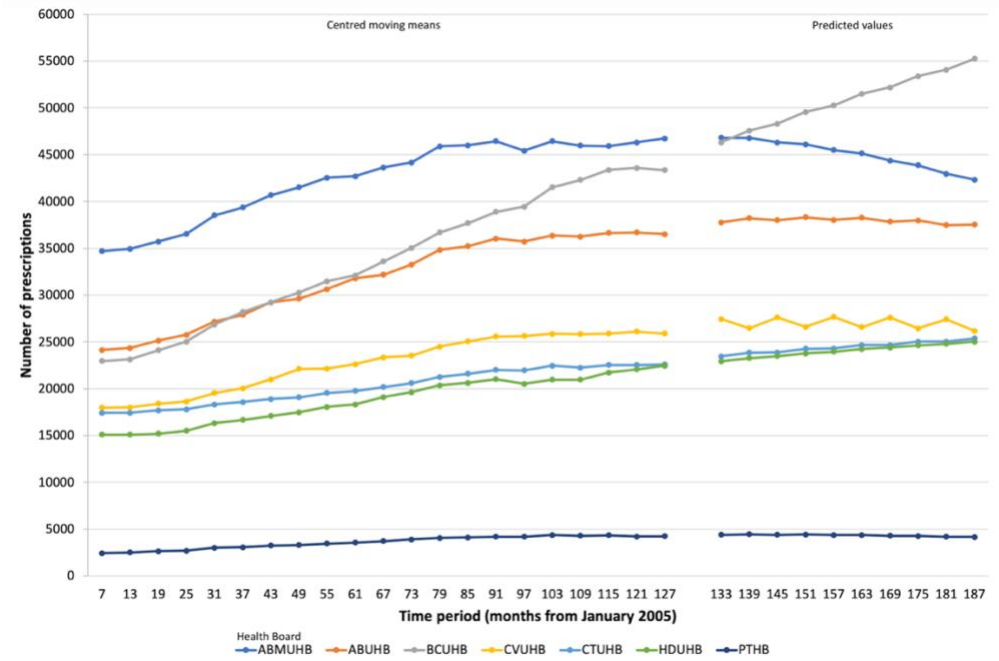


Figure E.27: Predicted trends in the number of opioid prescriptions issued to people in the 7 Health Boards (2nd order polynomial prediction)

ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Appendix F Healthcare resource utilisation associated with opioid prescribing and associated cost analysis

F.1 Metadata

Table F.1: Metadata used to extract data from main table of Phase 2 study using SQL coding or identifying columns in table

	COLUMN NAME	DESCRIPTION	Project Specific Detail
1	ALF_E	Anonymized linkage field	INTEGER: Including cases and their corresponding controls
2	GROUPS	Assigning a group number to each set of ALFS	INTEGER: Each set includes 1 Case-ALF and 4 corresponding controls
3	TYPE	Type of ALF	CASE CONTROL
4	AGE	Age at the 01-01-2016	>= 18
5	AGE_CAT	Age categories	1: [18-30] 2: [31-40] 3: [41-50] 4: [51-60] 5: [61-80] 6: 80+
6	GNDR_CD	Gender code	Each individual has a gender code allocated: 1=Male, 2=Female
7	OPIOID	They've received an opioid	Only applies to cases
8	MAX_PR_PERIOD _CAT	Maximum prescription period category for cases who have had opioids prescription in their WLGP record.	1: < 6 months 2: [6 months to 1) year 3: [1 to 2) year 4: [2 to 3) year 5: [3 to 4) year 6: [4 to 5) year 7: [5 to 6) year 8: [6 to 7) year 9: [7 to 8) year 10: [8 to 9) year 11: [9-10) year 12: Full 11 years
9	WLGP_REC_DUR_ CAT	Maximum duration of having continuous record of WLGP in the SAIL databank.	1: < 6 2: 6 months to 1 year 3: [1 to 2) year 4: [2 to 3) year 5: [3 to 4) year 6: [4 to 5) year 7: [5 to 6) year 8: [6 to 7) year 9: [7 to 8) year 10: [8 to 9) year 11: [9-10) year 12: Full 11 years
10	WIMD2011_5th	5th quintile for deprivation score	Value 1= most deprived
11	FIRST_OP_EVENT _DT	The earliest date of opioid prescription in the study period for cases	DATE

12	EDDS_ALL_ATT_CNT	Total number of A&E attendances regardless of the type of their attendance	Didn't use the code lists and just followed cases and controls to see how many time they've been into A&E **Note: If someone had more than one of the codes on the same date, then their EDDS_ATTENDANCE_CNT >= EDDS_ALL_ATT_CNT**
13	EDDS_ATTENDANCE_CNT	Number of A&E attendances for cases and controls	Using both ICD10 and EDDS specified codes **Note: For cases the number of attendances were count after their first opioid prescription all attendances for controls.**
14	OPDW_ATT_CNT	Total number of attendances at the outpatient	didn't use the code lists and just followed cases and controls to see how many time they've been into outpatient **Note: For cases the number of attendances were count after their first opioid prescription all attendances for controls.**
15	PEDW_ATT_CNT	Total number of hospital admissions	Didn't use the code lists and just followed cases and controls to see how many time they've been hospitalized **Note: For cases the number of attendances were count after their first opioid prescription all attendances for controls.**
16	DEPRESSION	Whether or not they had depression	0= no 1= yes
17	WEAK_OP	They've been administered weak opioid based on their GP record	0= no 1=yes
18	STRONG_OP	They've been administered strong opioid based on their GP record	0= no 1 = yes
Break down of EDDS attendance counts*(See final notes for instruction of how to use underlying table for breakdown of counts on other conditions) EDDS_ALL_ATT_CNT EDDS_ATTENDANCE_CNT **Note: For cases the number of attendances were count after their first opioid prescription all attendances for controls.**			
19	EDDS_AT_ADVERS_CNT	Number of A&E attendances for adverse reactions to drugs	Using provided categories on ICD10 codes

20	EDDS_AT_PAIN_CNT	Number of A&E attendances for pain	Using provided categories on ICD10 codes
21	EDDS_AT_INFEC_CNT	Number of A&E attendances for infection	Using provided categories on ICD10 codes
Break down of EDDS attendance counts based on 17 categories of EDDS specific code list **Note: For cases the number of attendances were count after their first opioid prescription all attendances for controls.**			
22	EDDS_AT_ENDOC	Number of A&E attendances for **endocrinological Conditions**	Using provided categories on A&E codes
23	EDDS_AT_FRACT	Number of A&E attendances for **Fracture**	Using provided categories on A&E codes
24	EDDS_AT_GAST	Number of A&E attendances for **Gastrointestinal Conditions**	Using provided categories on A&E codes
25	EDDS_AT_GUM	Number of A&E attendances for **Genito-Urinary Medicine**	Using provided categories on A&E codes
26	EDDS_AT_HEADINJ	Number of A&E attendances for **Head injury**	Using provided categories on A&E codes
27	EDDS_AT_JOINTINJ	Number of A&E attendances for **Joint Injury**	Using provided categories on A&E codes
28	EDDS_AT_LINFEC	Number of A&E attendances for local infection	Using provided categories on A&E codes
29	EDDS_AT_NC	Number of A&E attendances for Neurological Conditions	Using provided categories on A&E codes
30	EDDS_AT_PAIN	Number of A&E attendances for pain	Using provided categories on A&E codes
31	EDDS_AT_POIS	Number of A&E attendances for poisoning or overdose	Using provided categories on A&E codes
32	EDDS_AT_PSYC	Number of A&E attendances for Psychological/psychiatric conditions	Using provided categories on A&E codes
33	EDDS_AT_RESP	Number of A&E attendances for Respiratory Conditions	Using provided categories on A&E codes
34	EDDS_AT_RHEU	Number of A&E attendances for Rheumatologically Conditions	Using provided categories on A&E codes
35	EDDS_AT_SOC	Number of A&E attendances for Social Problems/Homelessness	Using provided categories on A&E codes
36	EDDS_AT_STINJ	Number of A&E attendances for Soft Tissue Injury	Using provided categories on A&E codes

37	EDDS_AT_UROLOG	Number of A&E attendances for Urological Conditions	Using provided categories on A&E codes
38	EDDS_AT_WOUND	Number of A&E attendances for Wound	Using provided categories on A&E codes
Break down of PEDW attendance counts based on 3 categories of ICD10 code list **Note: For cases the number of attendances were count after their first opioid prescription all attendances for controls.**			
39	PEDW_ADVERS_CNT	Number of PEDW attendances for adverse reactions to drugs	Using provided categories on ICD10 codes
40	PEDW_PAIN_CNT	Number of PEDW attendances for pain	Using provided categories on ICD10 codes
41	PEDW_INFEC_CNT	Number of PEDW attendances for infection	Using provided categories on ICD10 codes

F.2 Readcodes

Table F.2: Read codes for pain-related conditions used to extract case and control subjects

Medcode	Readcode	Readterm	cause	Readcode-V2-5dig	PREF_TERM_30	PREF_TERM_60
6736	16A..00	Stiff neck symptom	NECK	16A..	Stiff neck symptom	
1355	16A2.00	Stiff neck	NECK	16A2.	Stiff neck	
14882	16A3.00	Wry neck/torticollis	NECK	16A3.	Wry neck/torticollis	
16961	16A3.12	Wry neck symptom	NECK	16A3.		
41031	16AZ.00	Stiff neck symptom NOS	NECK	16AZ.	Stiff neck symptom NOS	
16183	1D21.00	Symptom: head/neck	NECK	1D21.	Symptom: head/neck	
6188	1D21.12	C/O - a neck symptom	NECK	1D21.		
7033	2H2D.00	O/E - neck joint abnormal	NECK	2H2D.	O/E - neck joint abnormal	
97899	2I21.00	O/E - sign - head/neck	NECK	2I21.	O/E - sign - head/neck	
59990	7G15.11	Sensory skin flap including to head or neck	NECK	7G15.	Sensory skin flap	
94954	7G15200	Local sensory skin flap to head or neck	NECK	7G152	Local sensory skin flap hd/nk	Local sensory skin flap to head or neck
61137	7G19.11	Local subcutaneous pedicle skin flap including to head/neck	NECK	7G19.	Local subcut pedicle skin flap	Local subcutaneous pedicle skin flap
59990	7G15.11	Sensory skin flap including to head or neck	NECK	7G15.	Sensory skin flap	
94954	7G15200	Local sensory skin flap to head or neck	NECK	7G152	Local sensory skin flap hd/nk	Local sensory skin flap to head or neck
61137	7G19.11	Local subcutaneous pedicle skin flap including to head/neck	NECK	7G19.	Local subcut pedicle skin flap	Local subcutaneous pedicle skin flap
57534	L331z00	Cord tight round neck NOS	NECK	L331z	Cord tight round neck NOS	
123	N131.00	Cervicalgia - pain in neck	NECK	N131.	Cervicalgia - pain in neck	
28823	N135.11	Contracture of neck	NECK	N135.	Torticollis unspecified	
9683	N135z11	Stiff neck NOS	NECK	N135z	Torticollis NOS	
2617	N135z12	Wry neck	NECK	N135z		
20994	N13y200	Crick in neck	NECK	N13y2	Crick in neck	
3640	N13z.00	Cervical and neck disorders NOS	NECK	N13z.	Cervical/neck disorder NOS	Cervical and neck disorders NOS
4698	N240500	Fibrositis of neck	NECK	N2405	Fibrositis of neck	
65125	PE1..11	Congenital wry neck	NECK	PE1..	Congen.sternomastoid torticol.	Congenital sternomastoid torticollis
16664	R04..00	[D]Head and neck symptoms	NECK	R04..	[D]Head and neck symptoms	
48124	R04z.00	[D]Other symptoms affecting head and neck	NECK	R04z.	[D]Head and neck, other sympt.	[D]Other symptoms affecting head and neck
15178	R04zz00	[D]Head and neck symptoms NOS	NECK	R04zz	[D]Head and neck symptoms NOS	
10252	S1...00	Fracture of neck and trunk	NECK	S1...	Fracture of neck and trunk	
3288	S10A.00	Fracture of neck	NECK	S10A.	Fracture of neck	
25284	S1z..00	Fracture of neck and trunk NOS	NECK	S1z..	Fracture of neck and trunk NOS	
99397	S261600	Open fracture thumb proximal phalanx, neck	NECK	S2616	Opn # thumb prox phlnx, neck	Open fracture thumb proximal phalanx, neck
2225	S30..00	Fracture of neck of femur	NECK	S30..	#Neck of femur	Fracture of neck of femur
41001	S490.12	Closed dislocation of neck	NECK	S490.	Cls dslc cervical spine	Closed dislocation cervical spine
93829	S491.12	Open dislocation of neck	NECK	S491.	Open dislocation cerv spine	Open dislocation cervical spine
2463	S570.00	Neck sprain	NECK	S570.	Neck sprain	
15212	S570000	Neck sprain, unspecified	NECK	S5700	Neck sprain, unspecified	
25576	S570z00	Neck sprain NOS	NECK	S570z	Neck sprain NOS	
8812	SD0y100	Superficial injury of neck NOS	NECK	SD0y1	Superficial injury of neck NOS	
69652	SD0z100	Superficial injury of neck NOS, infected	NECK	SD0z1	Superfic.inj.neck NOS+infectn.	Superficial injury of neck NOS, infected
36121	SDC0.00	Superficial injuries involving head with neck	NECK	SDC0.	Supfcl inj invlv head wth neck	Superficial injuries involving head with neck
20117	SE08.00	Other contusion neck	NECK	SE08.	Other contusion neck	
11724	SF0..00	Crush injury, face, scalp and neck	NECK	SF0..	Crush injury, face, scalp+neck	Crush injury, face, scalp and neck
12864	SF02.00	Crush injury, neck	NECK	SF02.	Crush injury, neck	
66769	SF02z00	Crush injury, neck NOS	NECK	SF02z	Crush injury, neck NOS	
96413	SF0z.00	Crush injury, face, scalp and neck NOS	NECK	SF0z.	Crush inj,face,scalp+neck NOS	Crush injury, face, scalp and neck NOS
51916	SH14900	Deep full thickness burn of neck without loss of body part	NECK	SH149	Deep F/T burn-neck-no BPL	Deep full thickness burn of neck without loss of body part

44249	SJ70.00	Head and neck superficial nerve injury	NECK	SJ70.	Head/neck superfic.nerve inj.	Head and neck superficial nerve injury
24486	SJ70.11	Head and neck superficial nerve injury	NECK	SJ70.		
35864	SJ70.12	Neck superficial nerve injury	NECK	SJ70.		
20930	SJ71.00	Injury of peripheral nerves of neck	NECK	SJ71.	Injury/periphrl nerves of neck	Injury of peripheral nerves of neck
23690	SJ8..00	Injury of nerves and spinal cord at neck level	NECK	SJ8..		
4446	SK10.00	Other face and neck injuries	NECK	SK10.	Other face/neck injuries	Other face and neck injuries
17360	SK10800	Injury of muscle and tendon at neck level	NECK	SK108	Injur/muscle+tendon/neck level	Injury of muscle and tendon at neck level
1192	SK10y00	Other neck injuries	NECK	SK10y	Other neck injuries	
14799	SK10z00	Other face and neck injuries NOS	NECK	SK10z	Other face/neck injuries NOS	Other face and neck injuries NOS
54854	SK1x100	Multiple superficial injuries of neck	NECK	SK1x1	Multipl superfic injuries/neck	Multiple superficial injuries of neck
21101	SK1x300	Multiple injuries of neck	NECK	SK1x3	Multiple injuries of neck	
32009	SR10.00	Fractures involving head with neck	NECK	SR10.	Fracture involv head with neck	Fractures involving head with neck
73786	SR10000	Closed fractures involving head with neck	NECK	SR100	Cls fract invol head with neck	Closed fractures involving head with neck
12327	SR20.00	Dislocations, sprains and strains involving head with neck	NECK	SR20.	Disloc,sprns+strns inv hd+neck	Dislocations, sprains and strains involving head with neck
48651	SR30.00	Crushing injuries involving head with neck	NECK	SR30.	Crush inj invlv head with neck	Crushing injuries involving head with neck
37326	Syu1.00	[X]Injuries to the neck	NECK	Syu1.	[X]Injuries to the neck	
58728	Syu1100	[X]Superficial injury of other parts of the neck	NECK	Syu11	[X]Superfic inj oth part neck	[X]Superficial injury of other parts of the neck
70825	Syu1200	[X]Superficial injury of neck, part unspecified	NECK	Syu12	[X]Superf inj neck, part unsp	[X]Superficial injury of neck, part unspecified
99936	Syu1600	[X]Fracture of other parts of neck	NECK	Syu16	[X]Fracture other parts neck	[X]Fracture of other parts of neck
53850	Syu1800	[X]Sprain/strain of joint/ligam of oth & unsp part of neck	NECK	Syu18	[X]Spr/str jt/lg ot/un pt neck	[X]Sprain/strain of joint/ligam of oth & unsp part of neck
102012	Syu1A00	[X]Injury of other and unspecified nerves of neck	NECK	Syu1A	[X]Inj oth unsp nerve of neck	[X]Injury of other and unspecified nerves of neck
68839	Syu1F00	[X]Other specified injuries of neck	NECK	Syu1F	[X]Oth specif inj of neck	[X]Other specified injuries of neck
97345	SyuLC00	[X]Sequelae of unspecified injury of neck and trunk	NECK	SyuLC	[X]Seq unspec injury neck+trnk	[X]Sequelae of unspecified injury of neck and trunk
36875	Z6G6200	Neck stretching	NECK	Z6G62		
63752	ZV48.00	[V]Head, neck or trunk problems	NECK	ZV48.	[V]Head, neck/ trunk problem	[V]Head, neck or trunk problems
7116	ZV48.12	[V]Problems with neck	NECK	ZV48.		
56003	ZV48500	[V]Sensory problem of neck or trunk	NECK	ZV485	[V]Neck/trunk sensory problem	[V]Sensory problem of neck or trunk

Medcode	Readcode	Readterm	cause	**Readcode-V2-5dig**	PREF_TERM_30
8120	14N3000	H/O Spinal surgery	SPINAL PAIN	14N30	H/O Spinal surgery
73015	2AD6.00	O/E - ciliospinal reflex -ve.	SPINAL PAIN	2AD6.	O/E - ciliospinal reflex -ve.
71673	7040	Partial extirpation of spinal cord	SPINAL PAIN	7040	
62660	7041000	Stereotactic chordotomy of spinal cord	SPINAL PAIN	70410	Stereotac chordotomy spin cord
15218	7041100	Open chordotomy of spinal cord NEC	SPINAL PAIN	70411	Open chordotomy spin cord NEC
57641	7041200	Myelotomy of spinal cord	SPINAL PAIN	70412	Myelotomy of spinal cord
21088	7042100	Percutaneous chordotomy of spinal cord	SPINAL PAIN	70421	Percut chordotomy spinal cord
5307	7043100	Closure of spinal myelomeningocele	SPINAL PAIN	70431	Closure spin myelomeningocele
29633	7043200	Closure of spinal meningocele	SPINAL PAIN	70432	Closure of spinal meningocele
1145	7047000	Spinal myelography NEC	SPINAL PAIN	70470	Spinal myelography NEC
66902	7047100	Spinal manometry	SPINAL PAIN	70471	Spinal manometry
67831	7048011	Destruction of lesion of spinal nerve root	SPINAL PAIN	70480	Extirpatn lesion spinal n root
21655	7048100	Rhizotomy of spinal nerve root	SPINAL PAIN	70481	Rhizotomy spinal nerve root
60506	7048400	Destruction of spinal nerve root NEC	SPINAL PAIN	70484	Destruct spinal nerve root NEC
33481	7049	Other destruction of spinal cord	SPINAL PAIN	7049	

97105	7049y00	Other specified destruction of spinal cord	SPINAL PAIN	7049y	Other destruct spinal cord OS
21288	7J3..11	Lumbar spinal cord operations	SPINAL PAIN	7J3..	Lumbar spine operations
63452	7J42300	Spinal extension traction for fracture of spine	SPINAL PAIN	7J423	Spinal extension traction #
15622	7J42500	Spinal traction for fracture of spine NEC	SPINAL PAIN	7J425	Spinal traction # spine NEC
42002	7J47900	Spinal probing	SPINAL PAIN	7J479	Spinal probing
16885	7J49.00	Denervation of spinal facet joint of vertebra	SPINAL PAIN	7J49.	Denervat spinal facet vertebra
45679	7J49100	Denervation of spinal facet joint of cervical vertebra NEC	SPINAL PAIN	7J491	Denerv cervic spinal facet NEC
65587	7J49300	Denervation of spinal facet joint of thoracic vertebra NEC	SPINAL PAIN	7J493	Denerv thoracic spin facet NEC
28261	7J49500	Denervation of spinal facet joint of lumbar vertebra NEC	SPINAL PAIN	7J495	Denerv lumbar spin facet NEC
70138	7J49y00	Denervation of spinal facet joint of vertebra OS	SPINAL PAIN	7J49y	Denerv vertebr spinal facet OS
40516	7J49z00	Denervation of spinal facet joint of vertebra NOS	SPINAL PAIN	7J49z	Denerv verteb spinal facet NOS
69837	A940.12	Syphilitic posterior spinal sclerosis	SPINAL PAIN	A940.	Tabes dorsalis - neurosyphilis
54143	B74y000	Lipoma of spinal column	SPINAL PAIN	B74y0	Lipoma of spinal column
70427	B74y100	Lipoma of spinal canal - extradural	SPINAL PAIN	B74y1	Lipoma of spine - extradural
64310	B74y200	Lipoma of spinal canal - intradural	SPINAL PAIN	B74y2	Lipoma of spine - intradural
70599	B74y300	Lipoma of spinal cord	SPINAL PAIN	B74y3	Lipoma of spinal cord
9544	B7F4000	Spinal meningioma	SPINAL PAIN	B7F40	Spinal meningioma
44774	B925100	Neoplasm of uncertain behaviour of spinal cord	SPINAL PAIN	B9251	Uncert. neopl. spinal cord
28567	F04..00	Intracranial and intraspinal abscesses	SPINAL PAIN	F04..	Intracranial / spinal abscess
15434	F041.00	Intraspinal abscess	SPINAL PAIN	F041.	Intraspinal abscess
73764	F041200	Subdural intraspinal abscess	SPINAL PAIN	F0412	Intraspinal abscess-subdural
60611	F041z00	Intraspinal abscess NOS	SPINAL PAIN	F041z	Intraspinal abscess NOS
23466	F04z.00	Intracranial or intraspinal abscess NOS	SPINAL PAIN	F04z.	Intracranial / spinal absc.NOS
95615	F150.11	Infantile spinal muscular atrophy	SPINAL PAIN	F150.	Werdnig - Hoffmann disease
9179	F151.00	Spinal muscular atrophy	SPINAL PAIN	F151.	Spinal muscular atrophy
70572	F151000	Unspecified spinal muscular atrophy	SPINAL PAIN	F1510	Spinal muscular atrophy unspec
70109	F151300	X-linked bulbo-spinal atrophy	SPINAL PAIN	F1513	X-linked bulbo-spinal atrophy
57632	F151z00	Spinal muscular atrophy NOS	SPINAL PAIN	F151z	Spinal muscular atrophy NOS
17194	F16..00	Other diseases of spinal cord	SPINAL PAIN	F16..	Other diseases of spinal cord
17216	F161000	Myelopathy due to acute infarction of spinal cord	SPINAL PAIN	F1610	Myelopathy-infarct spine cord
65630	F161100	Myelopathy due to arterial thrombosis of spinal cord	SPINAL PAIN	F1611	Myelopathy-thrombos spine cord
67980	F161200	Myelopathy due to oedema of spinal cord	SPINAL PAIN	F1612	Myelopathy-oedema spine cord
33535	F161500	Anterior spinal artery thrombosis	SPINAL PAIN	F1615	Ant spinal artery thrombosis
7736	F162.00	Subacute combined degeneration of spinal cord	SPINAL PAIN	F162.	Subacute combined cord degen.
69886	F201.00	Multiple sclerosis of the spinal cord	SPINAL PAIN	F201.	Multiple sclerosis-spinal cord
53396	F290y00	Other spinal puncture reaction	SPINAL PAIN	F290y	Other spinal puncture reaction
71885	F292100	Spinal meningeal adhesions	SPINAL PAIN	F2921	Adhesions - spinal meninges
51667	F292111	Spinal meningeal adhesions	SPINAL PAIN	F2921	
40237	F292300	Cyst of the spinal meninges	SPINAL PAIN	F2923	Cyst - spinal meninges
62548	Fyu0B00	[X]Intracranial+intraspinal abscess+granuloma in diseases CE	SPINAL PAIN	Fyu0B	[X]Intrcrn+intrspn ab+grn/d CE
101525	Fyu3200	[X]Subacute combined degeneration/spinal cord in diseases CE	SPINAL PAIN	Fyu32	[X]Subac cmb dgn/spn crd/ds CE
53754	FyuA700	[X]Other specified diseases of spinal cord	SPINAL PAIN	FyuA7	[X]Oth spcf disease/spinal crd
50241	G769.00	Anterior spinal and vertebral artery compression syndromes	SPINAL PAIN	G769.	Ant spin/vert art compr syndr
65804	L384100	Spinal/epidural anaesth-induced headache during puerp	SPINAL PAIN	L3841	Sp/ep anes-ind hdache dur puer
42755	L387.00	Spinal/epidural anesth-induced headache dur labour/delivery	SPINAL PAIN	L387.	Sp/epi anes-ind hdache,lab/del
24200	N101.00	Spinal enthesopathy	SPINAL PAIN	N101.	Spinal enthesopathy
45246	N12A.11	Post spinal surgery syndrome	SPINAL PAIN	N12A.	Postlaminectomy syndrome

69388	N130000	Idiopathic cervical spinal stenosis	SPINAL PAIN	N1300	Idiopathic Cx spinal stenosis
45296	N130100	Degenerative cervical spinal stenosis	SPINAL PAIN	N1301	Degenerativ Cx spinal stenosis
15331	N140.00	Spinal stenosis, excluding cervical region	SPINAL PAIN	N140.	Spinal stenosis excl.cervical
3370	N140.11	Spinal stenosis	SPINAL PAIN	N140.	
41147	N140000	Spinal stenosis of unspecified region	SPINAL PAIN	N1400	Spinal stenosis unspec.region
62612	N140100	Thoracic spinal stenosis	SPINAL PAIN	N1401	Thoracic spinal stenosis
9912	N140200	Lumbar spinal stenosis	SPINAL PAIN	N1402	Lumbar spinal stenosis
73730	N140400	Degenerative thoracic spinal stenosis	SPINAL PAIN	N1404	Degenerativ th spinal stenosis
98630	N140600	Thoracic spinal stenosis secondary to other disease	SPINAL PAIN	N1406	Th spin stenos due to oth dis
72614	N140700	Idiopathic lumbar spinal stenosis	SPINAL PAIN	N1407	Idiopathic lu spinal stenosis
43577	N140800	Degenerative lumbar spinal stenosis	SPINAL PAIN	N1408	Degenerativ lu spinal stenosis
93836	N140900	Iatrogenic lumbar spinal stenosis	SPINAL PAIN	N1409	Iatrogenic lu spinal stenosis
97870	N140A00	Lumbar spinal stenosis secondary to other disease	SPINAL PAIN	N140A	Lu spin stenos due to oth dis
35117	N140z00	Spinal stenosis NOS	SPINAL PAIN	N140z	Spinal stenosis NOS
18226	N14z.12	Spinal disorder NOS	SPINAL PAIN	N14z.	Back disorders NOS
100102	Nyu5B00	[X]Spinal osteochondrosis, unspecified	SPINAL PAIN	Nyu5B	[X]Spin osteochondrosis, unsp
53578	P111.00	Spinal hydromeningocele	SPINAL PAIN	P111.	Spinal hydromeningocele
6866	P113.00	Spinal meningocele	SPINAL PAIN	P113.	Spinal meningocele
53929	P113000	Spinal meningocele of unspecified site	SPINAL PAIN	P1130	Spinal meningocele-unspec.site
91600	P113200	Thoracic spinal meningocele	SPINAL PAIN	P1132	Spinal meningocele-thoracic
61862	P113300	Lumbar spinal meningocele	SPINAL PAIN	P1133	Spinal meningocele-lumbar
50365	P113z00	Spinal meningocele NOS	SPINAL PAIN	P113z	Spinal meningocele NOS
70266	P25..00	Other specified spinal cord anomalies	SPINAL PAIN	P25..	Other spec.spinal cord anomaly
48940	P252.00	Congenital tethering of spinal cord	SPINAL PAIN	P252.	Congen tethering spinal cord
95591	P25y.00	Other specified anomalies of spinal cord	SPINAL PAIN	P25y.	Spinal cord anomalies OS
45142	P25y112	Myelodysplasia of spinal cord	SPINAL PAIN	P25y1	Atelomyelia
45918	P25y200	Congenital anomaly of spinal meninges	SPINAL PAIN	P25y2	Spinal meninges congen.anomaly
73166	P25y400	Spinal cord hypoplasia	SPINAL PAIN	P25y4	Spinal cord hypoplasia
16164	P25z.00	Spinal cord anomalies NOS	SPINAL PAIN	P25z.	Spinal cord anomalies NOS
36974	P2y1.00	Congenital spinal cord anomaly	SPINAL PAIN	P2y1.	Congenital spinal cord anomaly
31857	Q204.00	Spine or spinal cord injury due to birth trauma	SPINAL PAIN	Q204.	Birth spine/spinal cord injury
100378	Q204z00	Spine or spinal cord injury due to birth trauma NOS	SPINAL PAIN	Q204z	Birth spine/cord injury NOS
8255	S10..00	Fracture of spine without mention of spinal cord injury	SPINAL PAIN	S10..	#Spine - no cord lesion
30058	S10..11	Fracture of transverse process spine - no spinal cord lesion	SPINAL PAIN	S10..	
4409	S10..12	Fracture of vertebra without spinal cord lesion	SPINAL PAIN	S10..	
42561	S100111	C1 vertebra closed fracture - no spinal cord lesion	SPINAL PAIN	S1001	Closed fracture atlas
33967	S100211	C2 vertebra closed fracture without spinal cord lesion	SPINAL PAIN	S1002	Closed fracture axis
52699	S100311	C3 vertebra closed fracture without spinal cord lesion	SPINAL PAIN	S1003	Clsd # third cerv vertebra
67358	S100411	C4 vertebra closed fracture without spinal cord lesion	SPINAL PAIN	S1004	Clsd # fourth cerv vertebra
34873	S100511	C5 vertebra closed fracture without spinal cord lesion	SPINAL PAIN	S1005	Clsd # fifth cerv vertebra
33503	S100611	C6 vertebra closed fracture without spinal cord lesion	SPINAL PAIN	S1006	Clsd # sixth cerv vertebra
38053	S100711	C7 vertebra closed fracture without spinal cord lesion	SPINAL PAIN	S1007	Clsd # seventh cerv vertebra
69098	S101111	C1 vertebra open fracture without spinal cord lesion	SPINAL PAIN	S1011	Open fracture atlas
97120	S101211	C2 vertebra open fracture without spinal cord lesion	SPINAL PAIN	S1012	Open fracture axis
60382	S101311	C3 vertebra open fracture without spinal cord lesion	SPINAL PAIN	S1013	Open # third cerv vertebra
99151	S101511	C5 vertebra open fracture without spinal cord lesion	SPINAL PAIN	S1015	Open # fifth cerv vertebra
62719	S101611	C6 vertebra open fracture without spinal cord lesion	SPINAL PAIN	S1016	Open # sixth cerv vertebra

59996	S101711	C7 vertebra open fracture without spinal cord lesion	SPINAL PAIN	S1017	Open # seventh cerv vert
34166	S10z.00	Fracture of spine without mention of spinal cord lesion NOS	SPINAL PAIN	S10z.	#Spine - no cord lesion - NOS
32063	S11..00	Fracture of spine with spinal cord lesion	SPINAL PAIN	S11..	#Spine + cord lesion
72324	S11..11	Fracture of transverse process of spine + spinal cord lesion	SPINAL PAIN	S11..	
43786	S11..12	Fracture of vertebra with spinal cord lesion	SPINAL PAIN	S11..	
62337	S110000	Cls spinal fracture with unspec cervical cord lesion, C1-4	SPINAL PAIN	S1100	Clsd # C1-C4 unspec cord les
100110	S110500	Cls spinal # with incomplete cervical cord lesion, C1-4 NOS	SPINAL PAIN	S1105	Clsd # C1-C4 incomp cord les
72711	S110600	Cls spinal fracture with unspec cervical cord lesion, C5-7	SPINAL PAIN	S1106	Clsd # C5-C7 unspec cord les
102735	S110700	Cls spinal fracture with complete cervcl cord lesion, C5-7	SPINAL PAIN	S1107	Clsd # C5-C7 complete cord les
96514	S110800	Cls spinal fracture with anterior cervcl cord lesion, C5-7	SPINAL PAIN	S1108	Clsd # C5-C7 ant cord lesion
101956	S110B00	Cls spinal # with incomplete cervical cord lesion, C5-7 NOS	SPINAL PAIN	S110B	Clsd # C5-C7 incomp cord les
69432	S111.00	Open fracture of cervical spine with spinal cord lesion	SPINAL PAIN	S111.	Open cervical #+cord lesion
35849	S112.00	Closed fracture of thoracic spine with spinal cord lesion	SPINAL PAIN	S112.	Closed thoracic #+cord lesion
48958	S112100	Cls spinal fracture wth complete thoracic cord lesion,T1-6	SPINAL PAIN	S1121	Cl sp #+cmpl thor crd lsn,T1-6
43091	S112600	Cls spinal fracture with unspec thoracic cord lesion, T7-12	SPINAL PAIN	S1126	Cl sp #+unsp thor cd lsn,T7-12
31545	S112700	Cls spinal fracture with complete thorac cord lesion, T7-12	SPINAL PAIN	S1127	Cl sp #+cmp thor crd lsn,T7-12
102043	S112A00	Cls spinal fracture with posterior thorac cord lesion, T7-12	SPINAL PAIN	S112A	Cl sp #+pst thor crd lsn,T7-12
70475	S112B00	Cls spinal # with incomplete thoracid cord lesion, T7-12 NOS	SPINAL PAIN	S112B	Cl # T7-12incomp cord lsn NOS
60615	S113.00	Open fracture of thoracic spine with spinal cord lesion	SPINAL PAIN	S113.	Open thoracic #+cord lesion
49567	S114000	Closed spinal fracture with unspecified lumbar cord lesion	SPINAL PAIN	S1140	Cls spn # + unsp lumb crd lesn
95529	S114100	Closed spinal fracture with complete lumbar cord lesion	SPINAL PAIN	S1141	Cls spn # + comp lumb crd lesn
73788	S114500	Closed spinal fracture with cauda equina lesion	SPINAL PAIN	S1145	Cls spn # + cauda equina lesn
94189	S115.00	Open fracture of lumbar spine with spinal cord lesion	SPINAL PAIN	S115.	Open lumbar # + cord lesion
96473	S117.00	Open fracture of sacrum with spinal cord lesion	SPINAL PAIN	S117.	Open sacral # + cord lesion
94584	S117300	Open fracture of sacrum with other spinal cord injury	SPINAL PAIN	S1173	Open sacral#+other cord injury
55195	S11z.00	Fracture of spine with spinal cord lesion NOS	SPINAL PAIN	S11z.	#Spine + cord lesion NOS
67389	S492300	Closed spinal dislocation with complete thoracic cord lesion	SPINAL PAIN	S4923	Cls spnl dsl+comp thrc crd lsn
30160	SJ...00	Nerve and spinal cord injuries	SPINAL PAIN	SJ...	Nerve/spinal cord injuries
11853	SJ...13	Spinal cord injuries	SPINAL PAIN	SJ...	
34835	SJ2..00	Spinal cord injury without evidence of spinal bone injury	SPINAL PAIN	SJ2..	Spinal cord inj.-no bone inj.
62286	SJ21.00	Thoracic cord injury without spinal bone injury	SPINAL PAIN	SJ21.	Thoracic cord inj.-no bone inj
59278	SJ21.11	Dorsal cord injury without spinal bone injury	SPINAL PAIN	SJ21.	
102775	SJ21z00	Thoracic cord injury without spinal bone injury, NOS	SPINAL PAIN	SJ21z	Thoracic cord inj.-no #, NOS
71521	SJ22.00	Lumbar cord injury without spinal bone injury	SPINAL PAIN	SJ22.	Cord inj.-lumbar-no bone inj.
58996	SJ2z.00	Spinal cord injury without spinal bone injury NOS	SPINAL PAIN	SJ2z.	Spinal cord inj.-no # NOS
30093	SJ3..00	Nerve roots and spinal plexus injuries	SPINAL PAIN	SJ3..	Nerve roots/spinal plexus inj.
26231	SJ3..11	Spinal plexus injury	SPINAL PAIN	SJ3..	
53904	SJ3z.00	Nerve root and spinal plexus injuries NOS	SPINAL PAIN	SJ3z.	Nerv.root/spinal plex.inj.NOS
23690	SJ8..00	Injury of nerves and spinal cord at neck level	SPINAL PAIN	SJ8..	Injur/nerv&spinl cord/neck lev
41935	SJ80.00	Concussion and oedema of cervical spinal cord	SPINAL PAIN	SJ80.	Concuss&oed/cervicl spinl cord
23778	SJ9..00	Injury of nerves and spinal cord at thorax level	SPINAL PAIN	SJ9..	Injur/nerv+spinl crd/thorx lev
100009	SJ90.00	Concussion and oedema of thoracic spinal cord	SPINAL PAIN	SJ90.	Concuss+oed/thoracic spinl crd
60687	SJA0.00	Concussion and oedema of lumbar spinal cord	SPINAL PAIN	SJA0.	Concuss+oed/lumbar spinal cord
3253	SJz..00	Nerve and spinal cord injury NOS	SPINAL PAIN	SJz..	Nerve/spinal cord injury NOS
97861	SP06300	Infected spinal fixation device	SPINAL PAIN	SP063	Infected spinal fixatn device
98874	Syu1900	[X]Other and unspecified injuries of cervical spinal cord	SPINAL PAIN	Syu19	[X]Oth unsp inj cerv spin cord

98833	Syu2B00	[X]Other and unspecified injuries of thoracic spinal cord	SPINAL PAIN	Syu2B	[X]Oth unsp inj thor spin cord
71966	Syu3800	[X]Other injury of lumbar spinal cord	SPINAL PAIN	Syu38	[X]Oth inj of lumb spin cord
52139	Zw04300	[Q] Central spinal stenosis	SPINAL PAIN	Zw043	[Q] Central spinal stenosis
91625	Zw04400	[Q] Lateral spinal stenosis	SPINAL PAIN	Zw044	[Q] Lateral spinal stenosis
94588	Zw04500	[Q] Central and lateral spinal stenosis	SPINAL PAIN	Zw045	[Q] Central + lat spin stenos
24796	16C4.00	Back pain worse on sneezing	BACK PAIN	16C4.	Back pain worse on sneezing
3763	16C5.00	C/O - low back pain	BACK PAIN	16C5.	C/O - low back pain
3324	16C6.00	Back pain without radiation NOS	BACK PAIN	16C6.	Back pain without radiat NOS
10231	16C9.00	Chronic low back pain	BACK PAIN	16C9.	Chronic low back pain
12189	16CA.00	Mechanical low back pain	BACK PAIN	16CA.	Mechanical low back pain
5476	N12..13	Acute back pain - disc	BACK PAIN	N12..	Intervertebral disc disorders
5916	N141.11	Acute back pain - thoracic	BACK PAIN	N141.	Pain in thoracic spine
154	N142.11	Low back pain	BACK PAIN	N142.	Pain in lumbar spine
5023	N142.13	Acute back pain - lumbar	BACK PAIN	N142.	
5840	N143.11	Acute back pain with sciatica	BACK PAIN	N143.	Sciatica
5923	N145.11	Acute back pain - unspecified	BACK PAIN	N145.	Backache, unspecified
6704	N145.12	Back pain, unspecified	BACK PAIN	N145.	
51894	A985300	Gonococcal spondylitis	ANKYLOSING SPONDYLITIS	A9853	Gonococcal spondylitis
42405	N045000	Juvenile ankylosing spondylitis	ANKYLOSING SPONDYLITIS	N0450	Juv ankylosing spondylitis
2184	N100.00	Ankylosing spondylitis	ANKYLOSING SPONDYLITIS	N100.	Ankylosing spondylitis
40946	N100.11	Marie - Strumpell spondylitis	ANKYLOSING SPONDYLITIS	N100.	
1963	N10z.00	Spondylitis NOS	ANKYLOSING SPONDYLITIS	N10z.	Spondylitis NOS
61090	N11y000	Brucella spondylitis	ANKYLOSING SPONDYLITIS	N11y0	Brucella spondylitis
49740	N11y100	Enterobacterial spondylitis	ANKYLOSING SPONDYLITIS	N11y1	Enterobacterial spondylitis

Medcode	Readcode	Readterm	cause	**Readcode-V2-5dig**	PREF_TERM_30	PREF_TERM_60
9760	14G2.00	H/O: osteoarthritis	OSTEOARTHRITIS	14G2.	H/O: osteoarthritis	
3057	N05..00	Osteoarthritis and allied disorders	OSTEOARTHRITIS	N05..	Osteoarthritis+allied disord.	Osteoarthritis and allied disorders
396	N05..11	Osteoarthritis	OSTEOARTHRITIS	N05..		
4353	N050.00	Generalised osteoarthritis - OA	OSTEOARTHRITIS	N050.	Generalised osteoarthritis-OA	Generalised osteoarthritis - OA
38631	N050000	Generalised osteoarthritis of unspecified site	OSTEOARTHRITIS	N0500	Generalised OA-site unspecif.	Generalised osteoarthritis of unspecified site
36327	N050100	Generalised osteoarthritis of the hand	OSTEOARTHRITIS	N0501	Generalised OA-hand	Generalised osteoarthritis of the hand
23676	N050200	Generalised osteoarthritis of multiple sites	OSTEOARTHRITIS	N0502	Generalised OA-multiple sites	Generalised osteoarthritis of multiple sites
34867	N050z00	Generalised osteoarthritis NOS	OSTEOARTHRITIS	N050z	Generalised osteoarthritis NOS	
32839	N051.00	Localised, primary osteoarthritis	OSTEOARTHRITIS	N051.	Local.primary osteoarthritis	Localised, primary osteoarthritis
54224	N051000	Localised, primary osteoarthritis of unspecified site	OSTEOARTHRITIS	N0510	Local.primary OA-site unspec.	Localised, primary osteoarthritis of unspecified site
24022	N051100	Localised, primary osteoarthritis of the shoulder region	OSTEOARTHRITIS	N0511	Local.primary OA-shoulder regn	Localised, primary osteoarthritis of the shoulder region
24217	N051200	Localised, primary osteoarthritis of the upper arm	OSTEOARTHRITIS	N0512	Local.primary OA-upper arm	Localised, primary osteoarthritis of the upper arm
34806	N051300	Localised, primary osteoarthritis of the forearm	OSTEOARTHRITIS	N0513	Local.primary OA-forearm	Localised, primary osteoarthritis of the forearm
21350	N051400	Localised, primary osteoarthritis of the hand	OSTEOARTHRITIS	N0514	Local.primary OA-hand	Localised, primary osteoarthritis of the hand
15839	N051500	Localised, primary osteoarthritis of the pelvic region/thigh	OSTEOARTHRITIS	N0515	Local.primary OA-pelvic/thigh	Localised, primary osteoarthritis of the pelvic region/thigh
21159	N051600	Localised, primary osteoarthritis of the lower leg	OSTEOARTHRITIS	N0516	Local.primary OA-lower leg	Localised, primary osteoarthritis of the lower leg
25793	N051700	Localised, primary osteoarthritis of the ankle and foot	OSTEOARTHRITIS	N0517	Local.primary OA-ankle/foot	Localised, primary osteoarthritis of the ankle and foot

20472	N051800	Localised, primary osteoarthritis of other specified site	OSTEOARTHRITIS	N0518	Local.primary OA-other specif	Localised, primary osteoarthritis of other specified site
24958	N051D00	Localised, primary osteoarthritis of the wrist	OSTEOARTHRITIS	N051D	Local prim osteoarth wrist	Localised, primary osteoarthritis of the wrist
28908	N051E00	Localised, primary osteoarthritis of toe	OSTEOARTHRITIS	N051E	Local prim osteoarth toe	Localised, primary osteoarthritis of toe
18602	N051F00	Localised, primary osteoarthritis of elbow	OSTEOARTHRITIS	N051F	Local prim osteoarth elbow	Localised, primary osteoarthritis of elbow
20660	N051z00	Localised, primary osteoarthritis NOS	OSTEOARTHRITIS	N051z	Localised primary OA NOS	Localised, primary osteoarthritis NOS
42045	N052.00	Localised, secondary osteoarthritis	OSTEOARTHRITIS	N052.	Local.secondary osteoarthritis	Localised, secondary osteoarthritis
68712	N052000	Localised, secondary osteoarthritis of unspecified site	OSTEOARTHRITIS	N0520	Local.secondary OA-site unsp.	Localised, secondary osteoarthritis of unspecified site
33574	N052100	Localised, secondary osteoarthritis of the shoulder region	OSTEOARTHRITIS	N0521	Local.secondary OA-shoulder	Localised, secondary osteoarthritis of the shoulder region
41088	N052200	Localised, secondary osteoarthritis of the upper arm	OSTEOARTHRITIS	N0522	Local.secondary OA-upper arm	Localised, secondary osteoarthritis of the upper arm
45815	N052300	Localised, secondary osteoarthritis of the forearm	OSTEOARTHRITIS	N0523	Local.secondary OA-forearm	Localised, secondary osteoarthritis of the forearm
23638	N052400	Localised, secondary osteoarthritis of the hand	OSTEOARTHRITIS	N0524	Local.secondary OA-hand	Localised, secondary osteoarthritis of the hand
44041	N052500	Localised, secondary osteoarthritis of pelvic region/thigh	OSTEOARTHRITIS	N0525	Local.secondary OA-pelv./thigh	Localised, secondary osteoarthritis of pelvic region/thigh
33479	N052600	Localised, secondary osteoarthritis of the lower leg	OSTEOARTHRITIS	N0526	Local.secondary OA-lower leg	Localised, secondary osteoarthritis of the lower leg
34035	N052700	Localised, secondary osteoarthritis of the ankle and foot	OSTEOARTHRITIS	N0527	Local.secondary OA-ankle/foot	Localised, secondary osteoarthritis of the ankle and foot
32891	N052800	Localised, secondary osteoarthritis of other specified site	OSTEOARTHRITIS	N0528	Local.secondary OA-other spec.	Localised, secondary osteoarthritis of other specified site
57912	N052z00	Localised, secondary osteoarthritis NOS	OSTEOARTHRITIS	N052z	Localised secondary OA NOS	Localised, secondary osteoarthritis NOS
34122	N053.00	Localised osteoarthritis, unspecified	OSTEOARTHRITIS	N053.	Localised OA unspecified	Localised osteoarthritis, unspecified
49545	N053000	Localised osteoarthritis, unspecified, of unspecified site	OSTEOARTHRITIS	N0530	Local.OA unsp.-site unspecif.	Localised osteoarthritis, unspecified, of unspecified site
15441	N053100	Localised osteoarthritis, unspecified, of shoulder region	OSTEOARTHRITIS	N0531	Local.OA unsp.-shoulder region	Localised osteoarthritis, unspecified, of shoulder region
59637	N053200	Localised osteoarthritis, unspecified, of the upper arm	OSTEOARTHRITIS	N0532	Local.OA unsp.-upper arm	Localised osteoarthritis, unspecified, of the upper arm
60537	N053300	Localised osteoarthritis, unspecified, of the forearm	OSTEOARTHRITIS	N0533	Local.OA unsp.-forearm	Localised osteoarthritis, unspecified, of the forearm
16242	N053400	Localised osteoarthritis, unspecified, of the hand	OSTEOARTHRITIS	N0534	Local.OA unsp.-hand	Localised osteoarthritis, unspecified, of the hand
20626	N053500	Localised osteoarthritis, unspecified, pelvic region/thigh	OSTEOARTHRITIS	N0535	Local.OA unsp.-pelvic/thigh	Localised osteoarthritis, unspecified, pelvic region/thigh
34804	N053600	Localised osteoarthritis, unspecified, of the lower leg	OSTEOARTHRITIS	N0536	Local.OA unsp.-lower leg	Localised osteoarthritis, unspecified, of the lower leg
1296	N053611	Patellofemoral osteoarthritis	OSTEOARTHRITIS	N0536		
4461	N053700	Localised osteoarthritis, unspecified, of the ankle and foot	OSTEOARTHRITIS	N0537	Local.OA unsp.-ankle/foot	Localised osteoarthritis, unspecified, of the ankle and foot
18112	N053800	Localised osteoarthritis, unspecified, of other spec site	OSTEOARTHRITIS	N0538	Local.OA unsp.-other specified	Localised osteoarthritis, unspecified, of other spec site
31200	N053z00	Localised osteoarthritis, unspecified, NOS	OSTEOARTHRITIS	N053z	Localised OA unspecified NOS	Localised osteoarthritis, unspecified, NOS
21528	N054.00	Oligoarticular osteoarthritis, unspecified	OSTEOARTHRITIS	N054.	Oligoarticular OA, unspecified	Oligoarticular osteoarthritis, unspecified
48214	N054000	Oligoarticular osteoarthritis, unspec, of unspecified sites	OSTEOARTHRITIS	N0540	Oligoartic OA, unsp-unsp sites	Oligoarticular osteoarthritis, unspec, of unspecified sites
52095	N054100	Oligoarticular osteoarthritis, unspecified, of shoulder	OSTEOARTHRITIS	N0541	Oligoartic OA, unspec-shoulder	Oligoarticular osteoarthritis, unspecified, of shoulder
97073	N054200	Oligoarticular osteoarthritis, unspecified, of upper arm	OSTEOARTHRITIS	N0542	Oligoartic OA, unspec-upp arm	Oligoarticular osteoarthritis, unspecified, of upper arm
59616	N054400	Oligoarticular osteoarthritis, unspecified, of hand	OSTEOARTHRITIS	N0544	Oligoartic OA, unspec-hand	Oligoarticular osteoarthritis, unspecified, of hand
68648	N054500	Oligoarticular osteoarthritis, unspecified, of pelvis/thigh	OSTEOARTHRITIS	N0545	Oligoartic OA, unspec-pelv/thi	Oligoarticular osteoarthritis, unspecified, of pelvis/thigh
41090	N054600	Oligoarticular osteoarthritis, unspecified, of lower leg	OSTEOARTHRITIS	N0546	Oligoartic OA, unspec-leg	Oligoarticular osteoarthritis, unspecified, of lower leg

72109	N054700	Oligoarticular osteoarthritis, unspecified, of ankle/foot	OSTEOARTHRITIS	N0547	Oligoartic OA, unspec-ank/foot	Oligoarticular osteoarthritis, unspecified, of ankle/foot
41985	N054800	Oligoarticular osteoarthritis, unspecified, other spec sites	OSTEOARTHRITIS	N0548	Oligoartic OA, unspec-oth site	Oligoarticular osteoarthritis, unspecified, other spec sites
57267	N054900	Oligoarticular osteoarthritis, unspecified, multiple sites	OSTEOARTHRITIS	N0549	Oligoartic OA, unspec-multiple	Oligoarticular osteoarthritis, unspecified, multiple sites
53858	N054z00	Osteoarthritis of more than one site, unspecified, NOS	OSTEOARTHRITIS	N054z	OA,1 site +,unspecified NOS	Osteoarthritis of more than one site, unspecified, NOS
5776	N05z.00	Osteoarthritis NOS	OSTEOARTHRITIS	N05z.	Osteoarthritis NOS	
35527	N05z000	Osteoarthritis NOS, of unspecified site	OSTEOARTHRITIS	N05z0	Osteoarthritis NOS-site unspec	Osteoarthritis NOS, of unspecified site
3147	N05z100	Osteoarthritis NOS, of shoulder region	OSTEOARTHRITIS	N05z1	Osteoarthritis NOS-shoulder	Osteoarthritis NOS, of shoulder region
50848	N05z200	Osteoarthritis NOS, of the upper arm	OSTEOARTHRITIS	N05z2	Osteoarthritis NOS-upper arm	Osteoarthritis NOS, of the upper arm
639	N05z211	Elbow osteoarthritis NOS	OSTEOARTHRITIS	N05z2		
24152	N05z300	Osteoarthritis NOS, of the forearm	OSTEOARTHRITIS	N05z3	Osteoarthritis NOS-forearm	Osteoarthritis NOS, of the forearm
15206	N05z311	Wrist osteoarthritis NOS	OSTEOARTHRITIS	N05z3		
658	N05z400	Osteoarthritis NOS, of the hand	OSTEOARTHRITIS	N05z4	Osteoarthritis NOS-hand	Osteoarthritis NOS, of the hand
4490	N05z411	Finger osteoarthritis NOS	OSTEOARTHRITIS	N05z4		
1959	N05z412	Thumb osteoarthritis NOS	OSTEOARTHRITIS	N05z4		
4967	N05z500	Osteoarthritis NOS, pelvic region/thigh	OSTEOARTHRITIS	N05z5	Osteoarthritis NOS-pelv./thigh	Osteoarthritis NOS, pelvic region/thigh
2209	N05z511	Hip osteoarthritis NOS	OSTEOARTHRITIS	N05z5		
15144	N05z600	Osteoarthritis NOS, of the lower leg	OSTEOARTHRITIS	N05z6	Osteoarthritis NOS-lower leg	Osteoarthritis NOS, of the lower leg
665	N05z611	Knee osteoarthritis NOS	OSTEOARTHRITIS	N05z6		
15447	N05z700	Osteoarthritis NOS, of ankle and foot	OSTEOARTHRITIS	N05z7	Osteoarthritis NOS-ankle/foot	Osteoarthritis NOS, of ankle and foot
52897	N05z711	Ankle osteoarthritis NOS	OSTEOARTHRITIS	N05z7		
1312	N05z712	Foot osteoarthritis NOS	OSTEOARTHRITIS	N05z7		
4878	N05z713	Toe osteoarthritis NOS	OSTEOARTHRITIS	N05z7		
15052	N05z800	Osteoarthritis NOS, other specified site	OSTEOARTHRITIS	N05z8	Osteoarthritis NOS-other spec	Osteoarthritis NOS, other specified site
5802	N05z900	Osteoarthritis NOS, of shoulder	OSTEOARTHRITIS	N05z9	Osteoarthritis NOS, shoulder	Osteoarthritis NOS, of shoulder
3814	N05zA00	Osteoarthritis NOS, of sternoclavicular joint	OSTEOARTHRITIS	N05zA	OA NOS-sternoclavicular joint	Osteoarthritis NOS, of sternoclavicular joint
2229	N05zB00	Osteoarthritis NOS, of acromioclavicular joint	OSTEOARTHRITIS	N05zB	OA NOS-acromioclavicular joint	Osteoarthritis NOS, of acromioclavicular joint
19713	N05zC00	Osteoarthritis NOS, of elbow	OSTEOARTHRITIS	N05zC	OA NOS-elbow	Osteoarthritis NOS, of elbow
65748	N05zD00	Osteoarthritis NOS, of distal radio-ulnar joint	OSTEOARTHRITIS	N05zD	OA NOS-dist radio-ulnar joint	Osteoarthritis NOS, of distal radio-ulnar joint
9649	N05zE00	Osteoarthritis NOS, of wrist	OSTEOARTHRITIS	N05zE	OA NOS-wrist	Osteoarthritis NOS, of wrist
7866	N05zF00	Osteoarthritis NOS, of MCP joint	OSTEOARTHRITIS	N05zF	OA NOS-MCP joint	Osteoarthritis NOS, of MCP joint
11032	N05zG00	Osteoarthritis NOS, of PIP joint of finger	OSTEOARTHRITIS	N05zG	OA NOS-PIP joint of finger	Osteoarthritis NOS, of PIP joint of finger
9681	N05zH00	Osteoarthritis NOS, of DIP joint of finger	OSTEOARTHRITIS	N05zH	OA NOS-DIP joint of finger	Osteoarthritis NOS, of DIP joint of finger
6812	N05zJ00	Osteoarthritis NOS, of hip	OSTEOARTHRITIS	N05zJ	OA NOS-hip	Osteoarthritis NOS, of hip
34023	N05zK00	Osteoarthritis NOS, of sacro-iliac joint	OSTEOARTHRITIS	N05zK	OA NOS-SI joint	Osteoarthritis NOS, of sacro-iliac joint
2487	N05zL00	Osteoarthritis NOS, of knee	OSTEOARTHRITIS	N05zL	Osteoarthritis NOS, of knee	
70425	N05zM00	Osteoarthritis NOS, of tibio-fibular joint	OSTEOARTHRITIS	N05zM	OA NOS tibio-fibular joint	Osteoarthritis NOS, of tibio-fibular joint
8202	N05zN00	Osteoarthritis NOS, of ankle	OSTEOARTHRITIS	N05zN	OA NOS-ankle	Osteoarthritis NOS, of ankle
40972	N05zP00	Osteoarthritis NOS, of subtalar joint	OSTEOARTHRITIS	N05zP	OA NOS-subtalar joint	Osteoarthritis NOS, of subtalar joint
55388	N05zQ00	Osteoarthritis NOS, of talonavicular joint	OSTEOARTHRITIS	N05zQ	OA NOS-talonavicular joint	Osteoarthritis NOS, of talonavicular joint
54350	N05zR00	Osteoarthritis NOS, of other tarsal joint	OSTEOARTHRITIS	N05zR	OA NOS-other tarsal joint	Osteoarthritis NOS, of other tarsal joint
6887	N05zS00	Osteoarthritis NOS, of 1st MTP joint	OSTEOARTHRITIS	N05zS	OA NOS-1st MTP joint	Osteoarthritis NOS, of 1st MTP joint
9010	N05zT00	Osteoarthritis NOS, of lesser MTP joint	OSTEOARTHRITIS	N05zT	OA NOS-lesser MTP joint	Osteoarthritis NOS, of lesser MTP joint
27834	N05zU00	Osteoarthritis NOS, of IP joint of toe	OSTEOARTHRITIS	N05zU	OA NOS-IP joint of toe	Osteoarthritis NOS, of IP joint of toe

27972	N05zz00	Osteoarthritis NOS	OSTEOARTHRITIS	N05zz	Osteoarthritis NOS	
7429	N11..12	Osteoarthritis of spine	OSTEOARTHRITIS	N11..	Spondylosis + allied disorders	Spondylosis and allied disorders
17092	N110.12	Osteoarthritis cervical spine	OSTEOARTHRITIS	N110.	Cervical spond.-no myelopathy	Cervical spondylosis without myelopathy
18826	N11D.00	Osteoarthritis of spine	OSTEOARTHRITIS	N11D.	Osteoarthritis of spine	
41378	N11D000	Osteoarthritis of cervical spine	OSTEOARTHRITIS	N11D0	Osteoarthritis cervical spine	Osteoarthritis of cervical spine
47024	N11D100	Osteoarthritis of thoracic spine	OSTEOARTHRITIS	N11D1	Osteoarthritis thoracic spine	Osteoarthritis of thoracic spine
22452	N11D200	Osteoarthritis of lumbar spine	OSTEOARTHRITIS	N11D2	Osteoarthritis of lumbar spine	
53184	N11D300	Osteoarthritis of spine NOS	OSTEOARTHRITIS	N11D3	Osteoarthritis of spine NOS	
829	N11z.11	Osteoarthritis spine	OSTEOARTHRITIS	N11z.	Spondylosis NOS	

Medcode	Readcode	Readterm	cause	**Readcode-V2-5dig**	PREF_TERM_30	PREF_TERM_60
476	M160.00	Psoriatic arthropathy	PSORIATIC ARTHROPATHY	M160.	Psoriatic arthropathy	
96880	M160.11	Psoriatic arthritis	PSORIATIC ARTHROPATHY	M160.		
32149	M160100	Distal interphalangeal psoriatic arthropathy	PSORIATIC ARTHROPATHY	M1601	Dist interphal psoriat arthrop	Distal interphalangeal psoriatic arthropathy
12500	M160z00	Psoriatic arthropathy NOS	PSORIATIC ARTHROPATHY	M160z	Psoriatic arthropathy NOS	
59107	Nyu1300	[X]Other psoriatic arthropathies	PSORIATIC ARTHROPATHY	Nyu13	[X]Oth psoriatic arthropathies	[X]Other psoriatic arthropathies
6639	14G1.00	H/O: rheumatoid arthritis	RHEUMATOID ARTHRITIS	14G1.	H/O: rheumatoid arthritis	
62401	F371200	Polyneuropathy in rheumatoid arthritis	RHEUMATOID ARTHRITIS	F3712	Polyneuropathy+rheumatoid arth	Polyneuropathy in rheumatoid arthritis
31209	F396400	Myopathy due to rheumatoid arthritis	RHEUMATOID ARTHRITIS	F3964	Myopathy+rheumatoid arthritis	Myopathy due to rheumatoid arthritis
27603	N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy	RHEUMATOID ARTHRITIS	N04..	Rheumatoid arthritis+similar	Rheumatoid arthritis and other inflammatory polyarthropathy
844	N040.00	Rheumatoid arthritis	RHEUMATOID ARTHRITIS	N040.	Rheumatoid arthritis	
44743	N040000	Rheumatoid arthritis of cervical spine	RHEUMATOID ARTHRITIS	N0400	Rheumatoid arthritis-Cx spine	Rheumatoid arthritis of cervical spine
44203	N040100	Other rheumatoid arthritis of spine	RHEUMATOID ARTHRITIS	N0401	Oth rheumatoid arthritis-spine	Other rheumatoid arthritis of spine
21358	N040200	Rheumatoid arthritis of shoulder	RHEUMATOID ARTHRITIS	N0402	Rheumatoid arthritis-shoulder	Rheumatoid arthritis of shoulder
100914	N040400	Rheumatoid arthritis of acromioclavicular joint	RHEUMATOID ARTHRITIS	N0404	Rheumatoid arthr-acromioclav j	Rheumatoid arthritis of acromioclavicular joint
59738	N040500	Rheumatoid arthritis of elbow	RHEUMATOID ARTHRITIS	N0405	Rheumatoid arthritis of elbow	
63365	N040600	Rheumatoid arthritis of distal radio-ulnar joint	RHEUMATOID ARTHRITIS	N0406	Rheumatoid arthritis-dist RUJ	Rheumatoid arthritis of distal radio-ulnar joint
48832	N040700	Rheumatoid arthritis of wrist	RHEUMATOID ARTHRITIS	N0407	Rheumatoid arthritis of wrist	
42299	N040800	Rheumatoid arthritis of MCP joint	RHEUMATOID ARTHRITIS	N0408	Rheumatoid arthritis-MCP joint	Rheumatoid arthritis of MCP joint
41941	N040900	Rheumatoid arthritis of PIP joint of finger	RHEUMATOID ARTHRITIS	N0409	Rheumatoid arthritis-PIPJ-fing	Rheumatoid arthritis of PIP joint of finger
63198	N040A00	Rheumatoid arthritis of DIP joint of finger	RHEUMATOID ARTHRITIS	N040A	Rheumatoid arthritis-DIPJ-fing	Rheumatoid arthritis of DIP joint of finger
49067	N040B00	Rheumatoid arthritis of hip	RHEUMATOID ARTHRITIS	N040B	Rheumatoid arthritis of hip	
100776	N040C00	Rheumatoid arthritis of sacro-iliac joint	RHEUMATOID ARTHRITIS	N040C	Rheumatoid arthritis of SIJ	Rheumatoid arthritis of sacro-iliac joint
50863	N040D00	Rheumatoid arthritis of knee	RHEUMATOID ARTHRITIS	N040D	Rheumatoid arthritis of knee	
51239	N040F00	Rheumatoid arthritis of ankle	RHEUMATOID ARTHRITIS	N040F	Rheumatoid arthritis of ankle	
73619	N040G00	Rheumatoid arthritis of subtalar joint	RHEUMATOID ARTHRITIS	N040G	Rheumatoid arthr-subtalar jnt	Rheumatoid arthritis of subtalar joint
70658	N040H00	Rheumatoid arthritis of talonavicular joint	RHEUMATOID ARTHRITIS	N040H	Rheumatoid arthr-talonav joint	Rheumatoid arthritis of talonavicular joint
71784	N040J00	Rheumatoid arthritis of other tarsal joint	RHEUMATOID ARTHRITIS	N040J	Rheumatoid arthr-oth tarsal jt	Rheumatoid arthritis of other tarsal joint
51238	N040K00	Rheumatoid arthritis of 1st MTP joint	RHEUMATOID ARTHRITIS	N040K	Rheumatoid arthr-1st MTP joint	Rheumatoid arthritis of 1st MTP joint
99414	N040L00	Rheumatoid arthritis of lesser MTP joint	RHEUMATOID ARTHRITIS	N040L	Rheumatoid arthr-lesser MTP jt	Rheumatoid arthritis of lesser MTP joint
6916	N040P00	Seronegative rheumatoid arthritis	RHEUMATOID ARTHRITIS	N040P	Seronegative rheumat arthritis	Seronegative rheumatoid arthritis
31054	N040S00	Rheumatoid arthritis - multiple joint	RHEUMATOID ARTHRITIS	N040S	Rheumat arthr - multiple joint	Rheumatoid arthritis - multiple joint
8350	N040T00	Flare of rheumatoid arthritis	RHEUMATOID ARTHRITIS	N040T	Flare of rheumatoid arthritis	
4186	N043.00	Juvenile rheumatoid arthritis - Stills disease	RHEUMATOID ARTHRITIS	N043.	Juvenile R.A.- Still's disease	Juvenile rheumatoid arthritis - Still's disease
47831	N043100	Acute polyarticular juvenile rheumatoid arthritis	RHEUMATOID ARTHRITIS	N0431	Acute polyartic.juvenile R.A.	Acute polyarticular juvenile rheumatoid arthritis

21533	N043200	Pauciarticular juvenile rheumatoid arthritis	RHEUMATOID ARTHRITIS	N0432	Pauciarticular juvenile R.A.	Pauciarticular juvenile rheumatoid arthritis
36276	N043300	Monarticular juvenile rheumatoid arthritis	RHEUMATOID ARTHRITIS	N0433	Monarticular juvenile R.A.	Monarticular juvenile rheumatoid arthritis
27557	N043z00	Juvenile rheumatoid arthritis NOS	RHEUMATOID ARTHRITIS	N043z	Juvenile rheumatoid arthr.NOS	Juvenile rheumatoid arthritis NOS
31360	N045500	Juvenile rheumatoid arthritis	RHEUMATOID ARTHRITIS	N0455	Juvenile rheumatoid arthritis	
9707	N047.00	Seropositive errosive rheumatoid arthritis	RHEUMATOID ARTHRITIS	N047.	Seropositive errosive RA	Seropositive errosive rheumatoid arthritis
12019	N04X.00	Seropositive rheumatoid arthritis, unspecified	RHEUMATOID ARTHRITIS	N04X.	Seroposit rheum arthr, unsp	Seropositive rheumatoid arthritis, unspecified
28853	N04y012	Fibrosing alveolitis associated with rheumatoid arthritis	RHEUMATOID ARTHRITIS	N04y0	Rheumatoid lung	
70221	Nyu1200	[X]Other specified rheumatoid arthritis	RHEUMATOID ARTHRITIS	Nyu12	[X]Oth spcf rheumatd arthritis	[X]Other specified rheumatoid arthritis
56202	Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified	RHEUMATOID ARTHRITIS	Nyu1G	[X]Seroposit rheum arthr, unsp	[X]Seropositive rheumatoid arthritis, unspecified

Readcode-V2-5dig	PREF_TERM_30	PREF_TERM_60	**Readcode-V3-5dig**	TERM_ID	TERM_30
X75rx	Y7Coo	Fibromyalgia	N239.	Fibromyalgia	
N2401	Y7Cor	Fibrositis unspecified	N248.	Fibromyalgia	
N2405	YaY8a	Fibrositis of neck	N2480	Myofascial pain syndrome	
N2406	YaY8b	Fibrositis arm	N2481	Piriformis syndrome	
Xa01F	Ya0tZ	Chronic fatigue syndrome	F286.	Chronic fatigue syndrome	
XaPoo	YasR0	Severe chronic fatigue syndrome	F2860	Mild chronic fatigue syndrome	
XaPon	YasQz	Moderate chronic fatigue syndrome	F2861	Moderate chronic fatigue syndrome	
XaPom	YasQy	Mild chronic fatigue syndrome	F2862	Severe chronic fatigue syndrome	
XaPom	YasQy	Mild chronic fatigue syndrome			

Medcode	Readcode	Readterm	cause	**Readcode-V2-5dig**	PREF_TERM_30
16481	1475	H/O: trigeminal neuralgia	TRIGEMINAL NEURALGIA	1475	
11498	A531200	Postherpetic trigeminal neuralgia	TRIGEMINAL NEURALGIA	A5312	Postherpetic trigem.neuralgia
7584	F300.00	Post-herpetic trigeminal neuralgia	TRIGEMINAL NEURALGIA	F300.	Post-herpetic trigem.neuralgia
1541	F301.00	Other specified trigeminal neuralgia	TRIGEMINAL NEURALGIA	F301.	Trigeminal neuralgia OS
6581	F301z00	Trigeminal neuralgia NOS	TRIGEMINAL NEURALGIA	F301z	Trigeminal neuralgia NOS
9193	F336.00	Phantom limb syndrome	PHANTOM LIMB PAIN	F336.	Phantom limb syndrome
18016	F336000	Phantom limb syndrome with pain	PHANTOM LIMB PAIN	F3360	Phantom limb syndrome wth pain
54894	F336100	Phantom limb syndrome without pain	PHANTOM LIMB PAIN	F3361	Phantom limb syn w'out pain
1598	A531.11	Post-herpetic neuralgia	POST HERPETIC NEURALGIA	A531.	Herpes zoster+other CNS compl.
17180	A531500	Postzoster neuralgia	POST HERPETIC NEURALGIA	A5315	Postzoster neuralgia
10223	A531511	Postherpetic neuralgia	POST HERPETIC NEURALGIA	A5315	
7795	C106.12	Diabetes mellitus with neuropathy	DIABETIC NEUROPATHY	C106.	Diab.mell. with neuropathy
16491	C106.13	Diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C106.	
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy	DIABETIC NEUROPATHY	C108B	IDDM with mononeuropathy
99231	C108B11	Type I diabetes mellitus with mononeuropathy	DIABETIC NEUROPATHY	C108B	
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C108C	IDDM with polyneuropathy
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy	DIABETIC NEUROPATHY	C109A	NIDDM with mononeuropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy	DIABETIC NEUROPATHY	C109A	
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C109B	NIDDM with polyneuropathy
47409	C109B11	Type II diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C109B	
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy	DIABETIC NEUROPATHY	C10EB	Type 1 diab mell + mononeurop
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C10EC	Type 1 diab mell + polyneurop
91943	C10EC11	Type I diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C10EC	
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C10EC	
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy	DIABETIC NEUROPATHY	C10FA	Type 2 diab mell mononeurop
95351	C10FA11	Type II diabetes mellitus with mononeuropathy	DIABETIC NEUROPATHY	C10FA	

18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C10FB	Type 2 diab mell + polyneurop
50527	C10FB11	Type II diabetes mellitus with polyneuropathy	DIABETIC NEUROPATHY	C10FB	
17067	F171100	Autonomic neuropathy due to diabetes	DIABETIC NEUROPATHY	F1711	Autonomic neuropathy-diabetes
31790	F372.00	Polyneuropathy in diabetes	DIABETIC NEUROPATHY	F372.	Polyneuropathy in diabetes
5002	F372.11	Diabetic polyneuropathy	DIABETIC NEUROPATHY	F372.	
2342	F372.12	Diabetic neuropathy	DIABETIC NEUROPATHY	F372.	
48078	F372000	Acute painful diabetic neuropathy	DIABETIC NEUROPATHY	F3720	Acute painful diab neuropathy
35785	F372100	Chronic painful diabetic neuropathy	DIABETIC NEUROPATHY	F3721	Chron painful diab neuropathy
24571	F372200	Asymptomatic diabetic neuropathy	DIABETIC NEUROPATHY	F3722	Asymptomatic diab neuropathy
37315	F3y0.00	Diabetic mononeuropathy	DIABETIC NEUROPATHY	F3y0.	Diabetic mononeuropathy

READ_VRS	PAIN_CAT	CODE_CAT	**READ_CD**	TERM_30	TERM_60
V2	NECK	NECK	16A..	Stiff neck symptom	
V2	NECK	NECK	16A2.	Stiff neck	
V2	NECK	NECK	16A3.	Wry neck/torticollis	
V2	NECK	NECK	16AZ.	Stiff neck symptom NOS	
V2	NECK	NECK	1D21.	Symptom: head/neck	
V2	NECK	NECK	2H2D.	O/E - neck joint abnormal	
V2	NECK	NECK	2I21.	O/E - sign - head/neck	
V2	NECK	NECK	7G15.	Sensory skin flap	
V2	NECK	NECK	7G152	Local sensory skin flap hd/nk	Local sensory skin flap to head or neck
V2	NECK	NECK	7G19.	Local subcut pedicle skin flap	Local subcutaneous pedicle skin flap
V2	NECK	NECK	L331z	Cord tight round neck NOS	
V2	NECK	NECK	N131.	Cervicalgia - pain in neck	
V2	NECK	NECK	N135.	Torticollis unspecified	
V2	NECK	NECK	N135z	Torticollis NOS	
V2	NECK	NECK	N13y2	Crick in neck	
V2	NECK	NECK	N13z.	Cervical/neck disorder NOS	Cervical and neck disorders NOS
V2	NECK	NECK	N2405	Fibrositis of neck	
V2	NECK	NECK	PE1..	Congen.sternomastoid torticol.	Congenital sternomastoid torticollis
V2	NECK	NECK	R04..	[D]Head and neck symptoms	
V2	NECK	NECK	R04z.	[D]Head and neck, other sympt.	[D]Other symptoms affecting head and neck
V2	NECK	NECK	R04zz	[D]Head and neck symptoms NOS	
V2	NECK	NECK	S1...	Fracture of neck and trunk	
V2	NECK	NECK	S10A.	Fracture of neck	
V2	NECK	NECK	S1z..	Fracture of neck and trunk NOS	
V2	NECK	NECK	S2616	Opn # thumb prox phlnx, neck	Open fracture thumb proximal phalanx, neck
V2	NECK	NECK	S30..	#Neck of femur	Fracture of neck of femur
V2	NECK	NECK	S490.	Cls dslc cervical spine	Closed dislocation cervical spine
V2	NECK	NECK	S491.	Open dislocation cerv spine	Open dislocation cervical spine
V2	NECK	NECK	S570.	Neck sprain	
V2	NECK	NECK	S5700	Neck sprain, unspecified	
V2	NECK	NECK	S570z	Neck sprain NOS	
V2	NECK	NECK	SD0y1	Superficial injury of neck NOS	

V2	NECK	NECK	SD0z1	Superfic.inj.neck NOS+infectn.	Superficial injury of neck NOS, infected
V2	NECK	NECK	SDC0.	Supfcl inj invlv head wth neck	Superficial injuries involving head with neck
V2	NECK	NECK	SE08.	Other contusion neck	
V2	NECK	NECK	SF0..	Crush injury, face, scalp+neck	Crush injury, face, scalp and neck
V2	NECK	NECK	SF02.	Crush injury, neck	
V2	NECK	NECK	SF02z	Crush injury, neck NOS	
V2	NECK	NECK	SF0z.	Crush inj,face,scalp+neck NOS	Crush injury, face, scalp and neck NOS
V2	NECK	NECK	SH149	Deep F/T burn-neck-no BPL	Deep full thickness burn of neck without loss of body part
V2	NECK	NECK	SJ70.	Head/neck superfic.nerve inj.	Head and neck superficial nerve injury
V2	NECK	NECK	SJ71.	Injury/periphrl nerves of neck	Injury of peripheral nerves of neck
V2	NECK	NECK	SK10.	Other face/neck injuries	Other face and neck injuries
V2	NECK	NECK	SK108	Injur/muscle+tendon/neck level	Injury of muscle and tendon at neck level
V2	NECK	NECK	SK10y	Other neck injuries	
V2	NECK	NECK	SK10z	Other face/neck injuries NOS	Other face and neck injuries NOS
V2	NECK	NECK	SK1x1	Multipl superfic injuries/neck	Multiple superficial injuries of neck
V2	NECK	NECK	SK1x3	Multiple injuries of neck	
V2	NECK	NECK	SR10.	Fracture involv head with neck	Fractures involving head with neck
V2	NECK	NECK	SR100	Cls fract invol head with neck	Closed fractures involving head with neck
V2	NECK	NECK	SR20.	Disloc,sprns+strns inv hd+neck	Dislocations, sprains and strains involving head with neck
V2	NECK	NECK	SR30.	Crush inj invlv head with neck	Crushing injuries involving head with neck
V2	NECK	NECK	Syu1.	[X]Injuries to the neck	
V2	NECK	NECK	Syu11	[X]Superfic inj oth part neck	[X]Superficial injury of other parts of the neck
V2	NECK	NECK	Syu12	[X]Superf inj neck, part unsp	[X]Superficial injury of neck, part unspecified
V2	NECK	NECK	Syu16	[X]Fracture other parts neck	[X]Fracture of other parts of neck
V2	NECK	NECK	Syu18	[X]Spr/str jt/lg ot/un pt neck	[X]Sprain/strain of joint/ligam of oth & unsp part of neck
V2	NECK	NECK	Syu1A	[X]Inj oth unsp nerve of neck	[X]Injury of other and unspecified nerves of neck
V2	NECK	NECK	Syu1F	[X]Oth specif inj of neck	[X]Other specified injuries of neck
V2	NECK	NECK	SyuLC	[X]Seq unspec injury neck+trnk	[X]Sequelae of unspecified injury of neck and trunk
V2	NECK	NECK	Z6G62		
V2	NECK	NECK	ZV48.	[V]Head, neck/ trunk problem	[V]Head, neck or trunk problems
V2	NECK	NECK	ZV485	[V]Neck/trunk sensory problem	[V]Sensory problem of neck or trunk
V2	BACK	SPINAL PAIN	14N30	H/O Spinal surgery	
V2	BACK	SPINAL PAIN	2AD6.	O/E - ciliospinal reflex -ve.	
V2	BACK	SPINAL PAIN	7040		
V2	BACK	SPINAL PAIN	70410	Stereotac chordotomy spin cord	Stereotactic chordotomy of spinal cord
V2	BACK	SPINAL PAIN	70411	Open chordotomy spin cord NEC	Open chordotomy of spinal cord NEC
V2	BACK	SPINAL PAIN	70412	Myelotomy of spinal cord	
V2	BACK	SPINAL PAIN	70421	Percut chordotomy spinal cord	Percutaneous chordotomy of spinal cord
V2	BACK	SPINAL PAIN	70431	Closure spin myelomeningocele	Closure of spinal myelomeningocele

V2	BACK	SPINAL PAIN	70432	Closure of spinal meningocele	
V2	BACK	SPINAL PAIN	70470	Spinal myelography NEC	
V2	BACK	SPINAL PAIN	70471	Spinal manometry	
V2	BACK	SPINAL PAIN	70480	Extirpatn lesion spinal n root	Extirpation of lesion of spinal nerve root
V2	BACK	SPINAL PAIN	70481	Rhizotomy spinal nerve root	Rhizotomy of spinal nerve root
V2	BACK	SPINAL PAIN	70484	Destruct spinal nerve root NEC	Destruction of spinal nerve root NEC
V2	BACK	SPINAL PAIN	7049		
V2	BACK	SPINAL PAIN	7049y	Other destruct spinal cord OS	Other specified destruction of spinal cord
V2	BACK	SPINAL PAIN	7J3..	Lumbar spine operations	
V2	BACK	SPINAL PAIN	7J423	Spinal extension traction #	Spinal extension traction for fracture of spine
V2	BACK	SPINAL PAIN	7J425	Spinal traction # spine NEC	Spinal traction for fracture of spine NEC
V2	BACK	SPINAL PAIN	7J479	Spinal probing	
V2	BACK	SPINAL PAIN	7J49.	Denervat spinal facet vertebra	Denervation of spinal facet joint of vertebra
V2	BACK	SPINAL PAIN	7J491	Denerv cervic spinal facet NEC	Denervation of spinal facet joint of cervical vertebra NEC
V2	BACK	SPINAL PAIN	7J493	Denerv thoracic spin facet NEC	Denervation of spinal facet joint of thoracic vertebra NEC
V2	BACK	SPINAL PAIN	7J495	Denerv lumbar spin facet NEC	Denervation of spinal facet joint of lumbar vertebra NEC
V2	BACK	SPINAL PAIN	7J49y	Denerv vertebr spinal facet OS	Denervation of spinal facet joint of vertebra OS
V2	BACK	SPINAL PAIN	7J49z	Denerv verteb spinal facet NOS	Denervation of spinal facet joint of vertebra NOS
V2	BACK	SPINAL PAIN	A940.	Tabes dorsalis - neurosyphilis	
V2	BACK	SPINAL PAIN	B74y0	Lipoma of spinal column	
V2	BACK	SPINAL PAIN	B74y1	Lipoma of spine - extradural	Lipoma of spinal canal - extradural
V2	BACK	SPINAL PAIN	B74y2	Lipoma of spine - intradural	Lipoma of spinal canal - intradural
V2	BACK	SPINAL PAIN	B74y3	Lipoma of spinal cord	
V2	BACK	SPINAL PAIN	B7F40	Spinal meningioma	
V2	BACK	SPINAL PAIN	B9251	Uncert. neopl. spinal cord	Neoplasm of uncertain behaviour of spinal cord
V2	BACK	SPINAL PAIN	F04..	Intracranial / spinal abscess	Intracranial and intraspinal abscesses
V2	BACK	SPINAL PAIN	F041.	Intraspinal abscess	
V2	BACK	SPINAL PAIN	F0412	Intraspinal abscess-subdural	Subdural intraspinal abscess
V2	BACK	SPINAL PAIN	F041z	Intraspinal abscess NOS	
V2	BACK	SPINAL PAIN	F04z.	Intracranial / spinal absc.NOS	Intracranial or intraspinal abscess NOS
V2	BACK	SPINAL PAIN	F150.	Werdnig - Hoffmann disease	
V2	BACK	SPINAL PAIN	F151.	Spinal muscular atrophy	
V2	BACK	SPINAL PAIN	F1510	Spinal muscular atrophy unspec	Unspecified spinal muscular atrophy
V2	BACK	SPINAL PAIN	F1513	X-linked bulbo-spinal atrophy	
V2	BACK	SPINAL PAIN	F151z	Spinal muscular atrophy NOS	
V2	BACK	SPINAL PAIN	F16..	Other diseases of spinal cord	
V2	BACK	SPINAL PAIN	F1610	Myelopathy-infarct spine cord	Myelopathy due to acute infarction of spinal cord
V2	BACK	SPINAL PAIN	F1611	Myelopathy-thrombos spine cord	Myelopathy due to arterial thrombosis of spinal cord
V2	BACK	SPINAL PAIN	F1612	Myelopathy-oedema spine cord	Myelopathy due to oedema of spinal cord

V2	BACK	SPINAL PAIN	F1615	Ant spinal artery thrombosis	Anterior spinal artery thrombosis
V2	BACK	SPINAL PAIN	F162.	Subacute combined cord degen.	Subacute combined degeneration of spinal cord
V2	BACK	SPINAL PAIN	F201.	Multiple sclerosis-spinal cord	Multiple sclerosis of the spinal cord
V2	BACK	SPINAL PAIN	F290y	Other spinal puncture reaction	
V2	BACK	SPINAL PAIN	F2921	Adhesions - spinal meninges	Spinal meningeal adhesions
V2	BACK	SPINAL PAIN	F2923	Cyst - spinal meninges	Cyst of the spinal meninges
V2	BACK	SPINAL PAIN	Fyu0B	[X]Intrcrn+intrspn ab+grn/d CE	[X]Intracranial+intraspinal abscess+granuloma in diseases CE
V2	BACK	SPINAL PAIN	Fyu32	[X]Subac cmb dgn/spn crd/ds CE	[X]Subacute combined degeneration/spinal cord in diseases CE
V2	BACK	SPINAL PAIN	FyuA7	[X]Oth spcf disease/spinal crd	[X]Other specified diseases of spinal cord
V2	BACK	SPINAL PAIN	G769.	Ant spin/vert art compr syndr	Anterior spinal and vertebral artery compression syndromes
V2	BACK	SPINAL PAIN	L3841	Sp/ep anes-ind hdache dur puer	Spinal/epidural anaesth-induced headache during puerp
V2	BACK	SPINAL PAIN	L387.	Sp/epi anes-ind hdache,lab/del	Spinal/epidural anesth-induced headache dur labour/delivery
V2	BACK	SPINAL PAIN	N101.	Spinal enthesopathy	
V2	BACK	SPINAL PAIN	N12A.	Postlaminectomy syndrome	
V2	BACK	SPINAL PAIN	N1300	Idiopathic Cx spinal stenosis	Idiopathic cervical spinal stenosis
V2	BACK	SPINAL PAIN	N1301	Degenerativ Cx spinal stenosis	Degenerative cervical spinal stenosis
V2	BACK	SPINAL PAIN	N140.	Spinal stenosis excl.cervical	Spinal stenosis, excluding cervical region
V2	BACK	SPINAL PAIN	N1400	Spinal stenosis unspec.region	Spinal stenosis of unspecified region
V2	BACK	SPINAL PAIN	N1401	Thoracic spinal stenosis	
V2	BACK	SPINAL PAIN	N1402	Lumbar spinal stenosis	
V2	BACK	SPINAL PAIN	N1404	Degenerativ th spinal stenosis	Degenerative thoracic spinal stenosis
V2	BACK	SPINAL PAIN	N1406	Th spin stenos due to oth dis	Thoracic spinal stenosis secondary to other disease
V2	BACK	SPINAL PAIN	N1407	Idiopathic lu spinal stenosis	Idiopathic lumbar spinal stenosis
V2	BACK	SPINAL PAIN	N1408	Degenerativ lu spinal stenosis	Degenerative lumbar spinal stenosis
V2	BACK	SPINAL PAIN	N1409	Iatrogenic lu spinal stenosis	Iatrogenic lumbar spinal stenosis
V2	BACK	SPINAL PAIN	N140A	Lu spin stenos due to oth dis	Lumbar spinal stenosis secondary to other disease
V2	BACK	SPINAL PAIN	N140z	Spinal stenosis NOS	
V2	BACK	SPINAL PAIN	N14z.	Back disorders NOS	
V2	BACK	SPINAL PAIN	Nyu5B	[X]Spin osteochondrosis, unsp	[X]Spinal osteochondrosis, unspecified
V2	BACK	SPINAL PAIN	P111.	Spinal hydromeningocele	
V2	BACK	SPINAL PAIN	P113.	Spinal meningocele	
V2	BACK	SPINAL PAIN	P1130	Spinal meningocele-unspec.site	Spinal meningocele of unspecified site
V2	BACK	SPINAL PAIN	P1132	Spinal meningocele-thoracic	Thoracic spinal meningocele
V2	BACK	SPINAL PAIN	P1133	Spinal meningocele-lumbar	Lumbar spinal meningocele
V2	BACK	SPINAL PAIN	P113z	Spinal meningocele NOS	
V2	BACK	SPINAL PAIN	P25..	Other spec.spinal cord anomaly	Other specified spinal cord anomalies
V2	BACK	SPINAL PAIN	P252.	Congen tethering spinal cord	Congenital tethering of spinal cord
V2	BACK	SPINAL PAIN	P25y.	Spinal cord anomalies OS	Other specified anomalies of spinal cord

V2	BACK	SPINAL PAIN	P25y1	Atelomyelia	
V2	BACK	SPINAL PAIN	P25y2	Spinal meninges congen.anomaly	Congenital anomaly of spinal meninges
V2	BACK	SPINAL PAIN	P25y4	Spinal cord hypoplasia	
V2	BACK	SPINAL PAIN	P25z.	Spinal cord anomalies NOS	
V2	BACK	SPINAL PAIN	P2y1.	Congenital spinal cord anomaly	
V2	BACK	SPINAL PAIN	Q204.	Birth spine/spinal cord injury	Spine or spinal cord injury due to birth trauma
V2	BACK	SPINAL PAIN	Q204z	Birth spine/cord injury NOS	Spine or spinal cord injury due to birth trauma NOS
V2	BACK	SPINAL PAIN	S10..	#Spine - no cord lesion	Fracture of spine without mention of spinal cord injury
V2	BACK	SPINAL PAIN	S1001	Closed fracture atlas	
V2	BACK	SPINAL PAIN	S1002	Closed fracture axis	
V2	BACK	SPINAL PAIN	S1003	Clsd # third cerv vertebra	Closed fracture of third cervical vertebra
V2	BACK	SPINAL PAIN	S1004	Clsd # fourth cerv vertebra	Closed fracture of fourth cervical vertebra
V2	BACK	SPINAL PAIN	S1005	Clsd # fifth cerv vertebra	Closed fracture of fifth cervical vertebra
V2	BACK	SPINAL PAIN	S1006	Clsd # sixth cerv vertebra	Closed fracture of sixth cervical vertebra
V2	BACK	SPINAL PAIN	S1007	Clsd # seventh cerv vertebra	Closed fracture of seventh cervical vertebra
V2	BACK	SPINAL PAIN	S1011	Open fracture atlas	
V2	BACK	SPINAL PAIN	S1012	Open fracture axis	
V2	BACK	SPINAL PAIN	S1013	Open # third cerv vertebra	Open fracture of third cervical vertebra
V2	BACK	SPINAL PAIN	S1015	Open # fifth cerv vertebra	Open fracture of fifth cervical vertebra
V2	BACK	SPINAL PAIN	S1016	Open # sixth cerv vertebra	Open fracture of sixth cervical vertebra
V2	BACK	SPINAL PAIN	S1017	Open # seventh cerv vert	Open fracture of seventh cervical vertebra
V2	BACK	SPINAL PAIN	S10z.	#Spine - no cord lesion - NOS	Fracture of spine without mention of spinal cord lesion NOS
V2	BACK	SPINAL PAIN	S11..	#Spine + cord lesion	Fracture of spine with spinal cord lesion
V2	BACK	SPINAL PAIN	S1100	Clsd # C1-C4 unspec cord les	Cls spinal fracture with unspec cervical cord lesion, C1-4
V2	BACK	SPINAL PAIN	S1105	Clsd # C1-C4 incomp cord les	Cls spinal # with incomplete cervical cord lesion, C1-4 NOS
V2	BACK	SPINAL PAIN	S1106	Clsd # C5-C7 unspec cord les	Cls spinal fracture with unspec cervical cord lesion, C5-7
V2	BACK	SPINAL PAIN	S1107	Clsd # C5-C7 complete cord les	Cls spinal fracture with complete cervcl cord lesion, C5-7
V2	BACK	SPINAL PAIN	S1108	Clsd # C5-C7 ant cord lesion	Cls spinal fracture with anterior cervcl cord lesion, C5-7
V2	BACK	SPINAL PAIN	S110B	Clsd # C5-C7 incomp cord les	Cls spinal # with incomplete cervical cord lesion, C5-7 NOS
V2	BACK	SPINAL PAIN	S111.	Open cervical #+cord lesion	Open fracture of cervical spine with spinal cord lesion
V2	BACK	SPINAL PAIN	S112.	Closed thoracic #+cord lesion	Closed fracture of thoracic spine with spinal cord lesion
V2	BACK	SPINAL PAIN	S1121	Cl sp #+cmpl thor crd lsn,T1-6	Cls spinal fracture wth complete thoracic cord lesion,T1-6
V2	BACK	SPINAL PAIN	S1126	Cl sp #+unsp thor cd lsn,T7-12	Cls spinal fracture with unspec thoracic cord lesion, T7-12
V2	BACK	SPINAL PAIN	S1127	Cl sp #+cmp thor crd lsn,T7-12	Cls spinal fracture with complete thorac cord lesion, T7-12

V2	BACK	SPINAL PAIN	S112A	Cl sp #+pst thor crd lsn,T7-12	Cls spinal fracture with posterior thorac cord lesion, T7-12
V2	BACK	SPINAL PAIN	S112B	Cl # T7-12incomp cord lsn NOS	Cls spinal # with incomplete thoracid cord lesion, T7-12 NOS
V2	BACK	SPINAL PAIN	S113.	Open thoracic #+cord lesion	Open fracture of thoracic spine with spinal cord lesion
V2	BACK	SPINAL PAIN	S1140	Cls spn # + unsp lumb crd lesn	Closed spinal fracture with unspecified lumbar cord lesion
V2	BACK	SPINAL PAIN	S1141	Cls spn # + comp lumb crd lesn	Closed spinal fracture with complete lumbar cord lesion
V2	BACK	SPINAL PAIN	S1145	Cls spn # + cauda equina lesn	Closed spinal fracture with cauda equina lesion
V2	BACK	SPINAL PAIN	S115.	Open lumbar # + cord lesion	Open fracture of lumbar spine with spinal cord lesion
V2	BACK	SPINAL PAIN	S117.	Open sacral # + cord lesion	Open fracture of sacrum with spinal cord lesion
V2	BACK	SPINAL PAIN	S1173	Open sacral#+other cord injury	Open fracture of sacrum with other spinal cord injury
V2	BACK	SPINAL PAIN	S11z.	#Spine + cord lesion NOS	Fracture of spine with spinal cord lesion NOS
V2	BACK	SPINAL PAIN	S4923	Cls spnl dsl+comp thrc crd lsn	Closed spinal dislocation with complete thoracic cord lesion
V2	BACK	SPINAL PAIN	SJ...	Nerve/spinal cord injuries	Nerve and spinal cord injuries
V2	BACK	SPINAL PAIN	SJ2..	Spinal cord inj.-no bone inj.	Spinal cord injury without evidence of spinal bone injury
V2	BACK	SPINAL PAIN	SJ21.	Thoracic cord inj.-no bone inj	Thoracic cord injury without spinal bone injury
V2	BACK	SPINAL PAIN	SJ21z	Thoracic cord inj.-no #, NOS	Thoracic cord injury without spinal bone injury, NOS
V2	BACK	SPINAL PAIN	SJ22.	Cord inj.-lumbar-no bone inj.	Lumbar cord injury without spinal bone injury
V2	BACK	SPINAL PAIN	SJ2z.	Spinal cord inj.-no # NOS	Spinal cord injury without spinal bone injury NOS
V2	BACK	SPINAL PAIN	SJ3..	Nerve roots/spinal plexus inj.	Nerve roots and spinal plexus injuries
V2	BACK	SPINAL PAIN	SJ3z.	Nerv.root/spinal plex.inj.NOS	Nerve root and spinal plexus injuries NOS
V2	BACK	SPINAL PAIN	SJ8..	Injur/nerv&spinl cord/neck lev	Injury of nerves and spinal cord at neck level
V2	BACK	SPINAL PAIN	SJ80.	Concuss&oed/cervicl spinl cord	Concussion and oedema of cervical spinal cord
V2	BACK	SPINAL PAIN	SJ9..	Injur/nerv+spinl crd/thorx lev	Injury of nerves and spinal cord at thorax level
V2	BACK	SPINAL PAIN	SJ90.	Concuss+oed/thoracic spinl crd	Concussion and oedema of thoracic spinal cord
V2	BACK	SPINAL PAIN	SJA0.	Concuss+oed/lumbar spinal cord	Concussion and oedema of lumbar spinal cord
V2	BACK	SPINAL PAIN	SJz..	Nerve/spinal cord injury NOS	Nerve and spinal cord injury NOS
V2	BACK	SPINAL PAIN	SP063	Infected spinal fixatn device	Infected spinal fixation device
V2	BACK	SPINAL PAIN	Syu19	[X]Oth unsp inj cerv spin cord	[X]Other and unspecified injuries of cervical spinal cord
V2	BACK	SPINAL PAIN	Syu2B	[X]Oth unsp inj thor spin cord	[X]Other and unspecified injuries of thoracic spinal cord
V2	BACK	SPINAL PAIN	Syu38	[X]Oth inj of lumb spin cord	[X]Other injury of lumbar spinal cord
V2	BACK	SPINAL PAIN	Zw043	[Q] Central spinal stenosis	
V2	BACK	SPINAL PAIN	Zw044	[Q] Lateral spinal stenosis	
V2	BACK	SPINAL PAIN	Zw045	[Q] Central + lat spin stenos	[Q] Central and lateral spinal stenosis
V2	BACK	BACK PAIN	16C4.	Back pain worse on sneezing	
V2	BACK	BACK PAIN	16C5.	C/O - low back pain	

V2	BACK	BACK PAIN	16C6.	Back pain without radiat NOS	Back pain without radiation NOS
V2	BACK	BACK PAIN	16C9.	Chronic low back pain	
V2	BACK	BACK PAIN	16CA.	Mechanical low back pain	
V2	BACK	BACK PAIN	N12..	Intervertebral disc disorders	
V2	BACK	BACK PAIN	N141.	Pain in thoracic spine	
V2	BACK	BACK PAIN	N142.	Pain in lumbar spine	
V2	BACK	BACK PAIN	N143.	Sciatica	
V2	BACK	BACK PAIN	N145.	Backache, unspecified	
V2	BACK	ANKYLOSING SPONDYLITIS	A9853	Gonococcal spondylitis	
V2	BACK	ANKYLOSING SPONDYLITIS	N0450	Juv ankylosing spondylitis	Juvenile ankylosing spondylitis
V2	BACK	ANKYLOSING SPONDYLITIS	N100.	Ankylosing spondylitis	
V2	BACK	ANKYLOSING SPONDYLITIS	N10z.	Spondylitis NOS	
V2	BACK	ANKYLOSING SPONDYLITIS	N11y0	Brucella spondylitis	
V2	BACK	ANKYLOSING SPONDYLITIS	N11y1	Enterobacterial spondylitis	
V2	OA	OSTEOARTHRITIS	14G2.	H/O: osteoarthritis	
V2	OA	OSTEOARTHRITIS	N05..	Osteoarthritis+allied disord.	Osteoarthritis and allied disorders
V2	OA	OSTEOARTHRITIS	N050.	Generalised osteoarthritis-OA	Generalised osteoarthritis - OA
V2	OA	OSTEOARTHRITIS	N0500	Generalised OA-site unspecif.	Generalised osteoarthritis of unspecified site
V2	OA	OSTEOARTHRITIS	N0501	Generalised OA-hand	Generalised osteoarthritis of the hand
V2	OA	OSTEOARTHRITIS	N0502	Generalised OA-multiple sites	Generalised osteoarthritis of multiple sites
V2	OA	OSTEOARTHRITIS	N050z	Generalised osteoarthritis NOS	
V2	OA	OSTEOARTHRITIS	N051.	Local.primary osteoarthritis	Localised, primary osteoarthritis
V2	OA	OSTEOARTHRITIS	N0510	Local.primary OA-site unspec.	Localised, primary osteoarthritis of unspecified site
V2	OA	OSTEOARTHRITIS	N0511	Local.primary OA-shoulder regn	Localised, primary osteoarthritis of the shoulder region
V2	OA	OSTEOARTHRITIS	N0512	Local.primary OA-upper arm	Localised, primary osteoarthritis of the upper arm
V2	OA	OSTEOARTHRITIS	N0513	Local.primary OA-forearm	Localised, primary osteoarthritis of the forearm
V2	OA	OSTEOARTHRITIS	N0514	Local.primary OA-hand	Localised, primary osteoarthritis of the hand
V2	OA	OSTEOARTHRITIS	N0515	Local.primary OA-pelvic/thigh	Localised, primary osteoarthritis of the pelvic region/thigh
V2	OA	OSTEOARTHRITIS	N0516	Local.primary OA-lower leg	Localised, primary osteoarthritis of the lower leg
V2	OA	OSTEOARTHRITIS	N0517	Local.primary OA-ankle/foot	Localised, primary osteoarthritis of the ankle and foot
V2	OA	OSTEOARTHRITIS	N0518	Local.primary OA-other specif	Localised, primary osteoarthritis of other specified site
V2	OA	OSTEOARTHRITIS	N051D	Local prim osteoarth wrist	Localised, primary osteoarthritis of the wrist
V2	OA	OSTEOARTHRITIS	N051E	Local prim osteoarth toe	Localised, primary osteoarthritis of toe
V2	OA	OSTEOARTHRITIS	N051F	Local prim osteoarth elbow	Localised, primary osteoarthritis of elbow
V2	OA	OSTEOARTHRITIS	N051z	Localised primary OA NOS	Localised, primary osteoarthritis NOS
V2	OA	OSTEOARTHRITIS	N052.	Local.secondary osteoarthritis	Localised, secondary osteoarthritis

V2	OA	OSTEOARTHRITIS	N0520	Local.secondary OA-site unsp.	Localised, secondary osteoarthritis of unspecified site
V2	OA	OSTEOARTHRITIS	N0521	Local.secondary OA-shoulder	Localised, secondary osteoarthritis of the shoulder region
V2	OA	OSTEOARTHRITIS	N0522	Local.secondary OA-upper arm	Localised, secondary osteoarthritis of the upper arm
V2	OA	OSTEOARTHRITIS	N0523	Local.secondary OA-forearm	Localised, secondary osteoarthritis of the forearm
V2	OA	OSTEOARTHRITIS	N0524	Local.secondary OA-hand	Localised, secondary osteoarthritis of the hand
V2	OA	OSTEOARTHRITIS	N0525	Local.secondary OA-pelv./thigh	Localised, secondary osteoarthritis of pelvic region/thigh
V2	OA	OSTEOARTHRITIS	N0526	Local.secondary OA-lower leg	Localised, secondary osteoarthritis of the lower leg
V2	OA	OSTEOARTHRITIS	N0527	Local.secondary OA-ankle/foot	Localised, secondary osteoarthritis of the ankle and foot
V2	OA	OSTEOARTHRITIS	N0528	Local.secondary OA-other spec.	Localised, secondary osteoarthritis of other specified site
V2	OA	OSTEOARTHRITIS	N052z	Localised secondary OA NOS	Localised, secondary osteoarthritis NOS
V2	OA	OSTEOARTHRITIS	N053.	Localised OA unspecified	Localised osteoarthritis, unspecified
V2	OA	OSTEOARTHRITIS	N0530	Local.OA unsp.-site unspecif.	Localised osteoarthritis, unspecified, of unspecified site
V2	OA	OSTEOARTHRITIS	N0531	Local.OA unsp.-shoulder region	Localised osteoarthritis, unspecified, of shoulder region
V2	OA	OSTEOARTHRITIS	N0532	Local.OA unsp.-upper arm	Localised osteoarthritis, unspecified, of the upper arm
V2	OA	OSTEOARTHRITIS	N0533	Local.OA unsp.-forearm	Localised osteoarthritis, unspecified, of the forearm
V2	OA	OSTEOARTHRITIS	N0534	Local.OA unsp.-hand	Localised osteoarthritis, unspecified, of the hand
V2	OA	OSTEOARTHRITIS	N0535	Local.OA unsp.-pelvic/thigh	Localised osteoarthritis, unspecified, pelvic region/thigh
V2	OA	OSTEOARTHRITIS	N0536	Local.OA unsp.-lower leg	Localised osteoarthritis, unspecified, of the lower leg
V2	OA	OSTEOARTHRITIS	N0537	Local.OA unsp.-ankle/foot	Localised osteoarthritis, unspecified, of the ankle and foot
V2	OA	OSTEOARTHRITIS	N0538	Local.OA unsp.-other specified	Localised osteoarthritis, unspecified, of other spec site
V2	OA	OSTEOARTHRITIS	N053z	Localised OA unspecified NOS	Localised osteoarthritis, unspecified, NOS
V2	OA	OSTEOARTHRITIS	N054.	Oligoarticular OA, unspecified	Oligoarticular osteoarthritis, unspecified
V2	OA	OSTEOARTHRITIS	N0540	Oligoartic OA, unsp-unsp sites	Oligoarticular osteoarthritis, unspec, of unspecified sites
V2	OA	OSTEOARTHRITIS	N0541	Oligoartic OA, unspec-shoulder	Oligoarticular osteoarthritis, unspecified, of shoulder
V2	OA	OSTEOARTHRITIS	N0542	Oligoartic OA, unspec-upp arm	Oligoarticular osteoarthritis, unspecified, of upper arm
V2	OA	OSTEOARTHRITIS	N0544	Oligoartic OA, unspec-hand	Oligoarticular osteoarthritis, unspecified, of hand
V2	OA	OSTEOARTHRITIS	N0545	Oligoartic OA, unspec-pelv/thi	Oligoarticular osteoarthritis, unspecified, of pelvis/thigh
V2	OA	OSTEOARTHRITIS	N0546	Oligoartic OA, unspec-leg	Oligoarticular osteoarthritis, unspecified, of lower leg
V2	OA	OSTEOARTHRITIS	N0547	Oligoartic OA, unspec-ank/foot	Oligoarticular osteoarthritis,

					unspecified, of ankle/foot
V2	OA	OSTEOARTHRITIS	N0548	Oligoartic OA, unspec-oth site	Oligoarticular osteoarthritis, unspecified, other spec sites
V2	OA	OSTEOARTHRITIS	N0549	Oligoartic OA, unspec-multiple	Oligoarticular osteoarthritis, unspecified, multiple sites
V2	OA	OSTEOARTHRITIS	N054z	OA,1 site +,unspecified NOS	Osteoarthritis of more than one site, unspecified, NOS
V2	OA	OSTEOARTHRITIS	N05z.	Osteoarthritis NOS	
V2	OA	OSTEOARTHRITIS	N05z0	Osteoarthritis NOS-site unspec	Osteoarthritis NOS, of unspecified site
V2	OA	OSTEOARTHRITIS	N05z1	Osteoarthritis NOS-shoulder	Osteoarthritis NOS, of shoulder region
V2	OA	OSTEOARTHRITIS	N05z2	Osteoarthritis NOS-upper arm	Osteoarthritis NOS, of the upper arm
V2	OA	OSTEOARTHRITIS	N05z3	Osteoarthritis NOS-forearm	Osteoarthritis NOS, of the forearm
V2	OA	OSTEOARTHRITIS	N05z4	Osteoarthritis NOS-hand	Osteoarthritis NOS, of the hand
V2	OA	OSTEOARTHRITIS	N05z5	Osteoarthritis NOS-pelv./thigh	Osteoarthritis NOS, pelvic region/thigh
V2	OA	OSTEOARTHRITIS	N05z6	Osteoarthritis NOS-lower leg	Osteoarthritis NOS, of the lower leg
V2	OA	OSTEOARTHRITIS	N05z7	Osteoarthritis NOS-ankle/foot	Osteoarthritis NOS, of ankle and foot
V2	OA	OSTEOARTHRITIS	N05z8	Osteoarthritis NOS-other spec	Osteoarthritis NOS, other specified site
V2	OA	OSTEOARTHRITIS	N05z9	Osteoarthritis NOS, shoulder	Osteoarthritis NOS, of shoulder
V2	OA	OSTEOARTHRITIS	N05zA	OA NOS-sternoclavicular joint	Osteoarthritis NOS, of sternoclavicular joint
V2	OA	OSTEOARTHRITIS	N05zB	OA NOS-acromioclavicular joint	Osteoarthritis NOS, of acromioclavicular joint
V2	OA	OSTEOARTHRITIS	N05zC	OA NOS-elbow	Osteoarthritis NOS, of elbow
V2	OA	OSTEOARTHRITIS	N05zD	OA NOS-dist radio-ulnar joint	Osteoarthritis NOS, of distal radio-ulnar joint
V2	OA	OSTEOARTHRITIS	N05zE	OA NOS-wrist	Osteoarthritis NOS, of wrist
V2	OA	OSTEOARTHRITIS	N05zF	OA NOS-MCP joint	Osteoarthritis NOS, of MCP joint
V2	OA	OSTEOARTHRITIS	N05zG	OA NOS-PIP joint of finger	Osteoarthritis NOS, of PIP joint of finger
V2	OA	OSTEOARTHRITIS	N05zH	OA NOS-DIP joint of finger	Osteoarthritis NOS, of DIP joint of finger
V2	OA	OSTEOARTHRITIS	N05zJ	OA NOS-hip	Osteoarthritis NOS, of hip
V2	OA	OSTEOARTHRITIS	N05zK	OA NOS-SI joint	Osteoarthritis NOS, of sacro-iliac joint
V2	OA	OSTEOARTHRITIS	N05zL	Osteoarthritis NOS, of knee	
V2	OA	OSTEOARTHRITIS	N05zM	OA NOS tibio-fibular joint	Osteoarthritis NOS, of tibio-fibular joint
V2	OA	OSTEOARTHRITIS	N05zN	OA NOS-ankle	Osteoarthritis NOS, of ankle
V2	OA	OSTEOARTHRITIS	N05zP	OA NOS-subtalar joint	Osteoarthritis NOS, of subtalar joint
V2	OA	OSTEOARTHRITIS	N05zQ	OA NOS-talonavicular joint	Osteoarthritis NOS, of talonavicular joint
V2	OA	OSTEOARTHRITIS	N05zR	OA NOS-other tarsal joint	Osteoarthritis NOS, of other tarsal joint
V2	OA	OSTEOARTHRITIS	N05zS	OA NOS-1st MTP joint	Osteoarthritis NOS, of 1st MTP joint
V2	OA	OSTEOARTHRITIS	N05zT	OA NOS-lesser MTP joint	Osteoarthritis NOS, of lesser MTP joint
V2	OA	OSTEOARTHRITIS	N05zU	OA NOS-IP joint of toe	Osteoarthritis NOS, of IP joint of toe
V2	OA	OSTEOARTHRITIS	N05zz	Osteoarthritis NOS	
V2	OA	OSTEOARTHRITIS	N11..	Spondylosis + allied disorders	Spondylosis and allied disorders
V2	OA	OSTEOARTHRITIS	N110.	Cervical spond.-no myelopathy	Cervical spondylosis without myelopathy
V2	OA	OSTEOARTHRITIS	N11D.	Osteoarthritis of spine	
V2	OA	OSTEOARTHRITIS	N11D0	Osteoarthritis cervical spine	Osteoarthritis of cervical spine

V2	OA	OSTEOARTHRITIS	N11D1	Osteoarthritis thoracic spine	Osteoarthritis of thoracic spine
V2	OA	OSTEOARTHRITIS	N11D2	Osteoarthritis of lumbar spine	
V2	OA	OSTEOARTHRITIS	N11D3	Osteoarthritis of spine NOS	
V2	OA	OSTEOARTHRITIS	N11z.	Spondylosis NOS	
V2	RA	PSORIATIC ARTHROPATHY	M160.	Psoriatic arthropathy	
V2	RA	PSORIATIC ARTHROPATHY	M1601	Dist interphal psoriat arthrop	Distal interphalangeal psoriatic arthropathy
V2	RA	PSORIATIC ARTHROPATHY	M160z	Psoriatic arthropathy NOS	
V2	RA	PSORIATIC ARTHROPATHY	Nyu13	[X]Oth psoriatic arthropathies	[X]Other psoriatic arthropathies
V2	RA	RHEUMATOID ARTHRITIS	14G1.	H/O: rheumatoid arthritis	
V2	RA	RHEUMATOID ARTHRITIS	F3712	Polyneuropathy+rheumatoid arth	Polyneuropathy in rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	F3964	Myopathy+rheumatoid arthritis	Myopathy due to rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	N04..	Rheumatoid arthritis+similar	Rheumatoid arthritis and other inflammatory polyarthropathy
V2	RA	RHEUMATOID ARTHRITIS	N040.	Rheumatoid arthritis	
V2	RA	RHEUMATOID ARTHRITIS	N0400	Rheumatoid arthritis-Cx spine	Rheumatoid arthritis of cervical spine
V2	RA	RHEUMATOID ARTHRITIS	N0401	Oth rheumatoid arthritis-spine	Other rheumatoid arthritis of spine
V2	RA	RHEUMATOID ARTHRITIS	N0402	Rheumatoid arthritis-shoulder	Rheumatoid arthritis of shoulder
V2	RA	RHEUMATOID ARTHRITIS	N0404	Rheumatoid arthr-acromioclav j	Rheumatoid arthritis of acromioclavicular joint
V2	RA	RHEUMATOID ARTHRITIS	N0405	Rheumatoid arthritis of elbow	
V2	RA	RHEUMATOID ARTHRITIS	N0406	Rheumatoid arthritis-dist RUJ	Rheumatoid arthritis of distal radio-ulnar joint
V2	RA	RHEUMATOID ARTHRITIS	N0407	Rheumatoid arthritis of wrist	
V2	RA	RHEUMATOID ARTHRITIS	N0408	Rheumatoid arthritis-MCP joint	Rheumatoid arthritis of MCP joint
V2	RA	RHEUMATOID ARTHRITIS	N0409	Rheumatoid arthritis-PIPJ-fing	Rheumatoid arthritis of PIP joint of finger
V2	RA	RHEUMATOID ARTHRITIS	N040A	Rheumatoid arthritis-DIPJ-fing	Rheumatoid arthritis of DIP joint of finger
V2	RA	RHEUMATOID ARTHRITIS	N040B	Rheumatoid arthritis of hip	
V2	RA	RHEUMATOID ARTHRITIS	N040C	Rheumatoid arthritis of SIJ	Rheumatoid arthritis of sacro-iliac joint
V2	RA	RHEUMATOID ARTHRITIS	N040D	Rheumatoid arthritis of knee	
V2	RA	RHEUMATOID ARTHRITIS	N040F	Rheumatoid arthritis of ankle	
V2	RA	RHEUMATOID ARTHRITIS	N040G	Rheumatoid arthr-subtalar jnt	Rheumatoid arthritis of subtalar joint
V2	RA	RHEUMATOID ARTHRITIS	N040H	Rheumatoid arthr-talonav joint	Rheumatoid arthritis of talonavicular joint
V2	RA	RHEUMATOID ARTHRITIS	N040J	Rheumatoid arthr-oth tarsal jt	Rheumatoid arthritis of other tarsal joint
V2	RA	RHEUMATOID ARTHRITIS	N040K	Rheumatoid arthr-1st MTP joint	Rheumatoid arthritis of 1st MTP joint
V2	RA	RHEUMATOID ARTHRITIS	N040L	Rheumatoid arthr-lesser MTP jt	Rheumatoid arthritis of lesser MTP joint
V2	RA	RHEUMATOID ARTHRITIS	N040P	Seronegative rheumat arthritis	Seronegative rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	N040S	Rheumat arthr - multiple joint	Rheumatoid arthritis - multiple joint
V2	RA	RHEUMATOID ARTHRITIS	N040T	Flare of rheumatoid arthritis	
V2	RA	RHEUMATOID ARTHRITIS	N043.	Juvenile R.A.- Still's disease	Juvenile rheumatoid arthritis - Still's disease
V2	RA	RHEUMATOID ARTHRITIS	N0431	Acute polyartic.juvenile R.A.	Acute polyarticular juvenile rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	N0432	Pauciarticular juvenile R.A.	Pauciarticular juvenile rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	N0433	Monarticular juvenile R.A.	Monarticular juvenile rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	N043z	Juvenile rheumatoid arthr.NOS	Juvenile rheumatoid arthritis NOS
V2	RA	RHEUMATOID ARTHRITIS	N0455	Juvenile rheumatoid arthritis	

V2	RA	RHEUMATOID ARTHRITIS	N047.	Seropositive errosive RA	Seropositive errosive rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	N04X.	Seroposit rheum arthr, unsp	Seropositive rheumatoid arthritis, unspecified
V2	RA	RHEUMATOID ARTHRITIS	N04y0	Rheumatoid lung	
V2	RA	RHEUMATOID ARTHRITIS	Nyu12	[X]Oth spcf rheumatd arthritis	[X]Other specified rheumatoid arthritis
V2	RA	RHEUMATOID ARTHRITIS	Nyu1G	[X]Seroposit rheum arthr, unsp	[X]Seropositive rheumatoid arthritis, unspecified
V3	FIBRO	FIBROMYALGIA	X75rx	Fibromyalgia	
V3	FIBRO	FIBROMYALGIA	N2401	Fibrositis unspecified	
V3	FIBRO	FIBROMYALGIA	N2405	Fibrositis of neck	
V3	FIBRO	FIBROMYALGIA	N2406	Fibrositis arm	
V3	FIBRO	FIBROMYALGIA	Xa01F	Chronic fatigue syndrome	
V3	FIBRO	FIBROMYALGIA	XaPoo	Severe chronic fatigue syndrome	
V3	FIBRO	FIBROMYALGIA	XaPon	Moderate chronic fatigue syndrome	
V3	FIBRO	FIBROMYALGIA	XaPom	Mild chronic fatigue syndrome	
V3	FIBRO	FIBROMYALGIA	XaPom	Mild chronic fatigue syndrome	
V2	FIBRO	FIBROMYALGIA	N239.	Fibromyalgia	
V2	FIBRO	FIBROMYALGIA	N248.	Fibromyalgia	
V2	FIBRO	FIBROMYALGIA	N2480	Myofascial pain syndrome	
V2	FIBRO	FIBROMYALGIA	N2481	Piriformis syndrome	
V2	FIBRO	FIBROMYALGIA	F286.	Chronic fatigue syndrome	
V2	FIBRO	FIBROMYALGIA	F2860	Mild chronic fatigue syndrome	
V2	FIBRO	FIBROMYALGIA	F2861	Moderate chronic fatigue syndrome	
V2	FIBRO	FIBROMYALGIA	F2862	Severe chronic fatigue syndrome	
V2	NEP	TRIGEMINAL NEURALGIA	1475		
V2	NEP	TRIGEMINAL NEURALGIA	A5312	Postherpetic trigem.neuralgia	Postherpetic trigeminal neuralgia
V2	NEP	TRIGEMINAL NEURALGIA	F300.	Post-herpetic trigem.neuralgia	Post-herpetic trigeminal neuralgia
V2	NEP	TRIGEMINAL NEURALGIA	F301.	Trigeminal neuralgia OS	Other specified trigeminal neuralgia
V2	NEP	TRIGEMINAL NEURALGIA	F301z	Trigeminal neuralgia NOS	
V2	NEP	PHANTOM LIMB PAIN	F336.	Phantom limb syndrome	
V2	NEP	PHANTOM LIMB PAIN	F3360	Phantom limb syndrome wth pain	Phantom limb syndrome with pain
V2	NEP	PHANTOM LIMB PAIN	F3361	Phantom limb syn w'out pain	Phantom limb syndrome without pain
V2	NEP	POST HERPETIC NEURALGIA	A531.	Herpes zoster+other CNS compl.	Herpes zoster with other central nervous system complication
V2	NEP	POST HERPETIC NEURALGIA	A5315	Postzoster neuralgia	
V2	NEP	DIABETIC NEUROPATHY	C106.	Diab.mell. with neuropathy	Diabetes mellitus with neurological manifestation
V2	NEP	DIABETIC NEUROPATHY	C108B	IDDM with mononeuropathy	Insulin dependent diabetes mellitus with mononeuropathy
V2	NEP	DIABETIC NEUROPATHY	C108C	IDDM with polyneuropathy	Insulin dependent diabetes mellitus with polyneuropathy
V2	NEP	DIABETIC NEUROPATHY	C109A	NIDDM with mononeuropathy	Non-insulin dependent diabetes mellitus with mononeuropathy
V2	NEP	DIABETIC NEUROPATHY	C109B	NIDDM with polyneuropathy	Non-insulin dependent diabetes mellitus with polyneuropathy
V2	NEP	DIABETIC NEUROPATHY	C10EB	Type 1 diab mell + mononeurop	Type 1 diabetes mellitus with mononeuropathy
V2	NEP	DIABETIC NEUROPATHY	C10EC	Type 1 diab mell + polyneurop	Type 1 diabetes mellitus with polyneuropathy
V2	NEP	DIABETIC NEUROPATHY	C10FA	Type 2 diab mell mononeurop	Type 2 diabetes mellitus with mononeuropathy

V2	NEP	DIABETIC NEUROPATHY	C10FB	Type 2 diab mell + polyneurop	Type 2 diabetes mellitus with polyneuropathy
V2	NEP	DIABETIC NEUROPATHY	F1711	Autonomic neuropathy-diabetes	Autonomic neuropathy due to diabetes
V2	NEP	DIABETIC NEUROPATHY	F372.	Polyneuropathy in diabetes	
V2	NEP	DIABETIC NEUROPATHY	F3720	Acute painful diab neuropathy	Acute painful diabetic neuropathy
V2	NEP	DIABETIC NEUROPATHY	F3721	Chron painful diab neuropathy	Chronic painful diabetic neuropathy
V2	NEP	DIABETIC NEUROPATHY	F3722	Asymptomatic diab neuropathy	Asymptomatic diabetic neuropathy
V2	NEP	DIABETIC NEUROPATHY	F3y0.	Diabetic mononeuropathy	

F.3 Two-way ANOVA for Healthcare utilisation

Test of dependence between CaseControl and Gender - number of attendances in primary care

Descriptive Statistics

Dependent \ GP_DAYS

CASECONTROL		Mean	Std. Deviation	N
.00	1	26.82	52.733	1092228
	2	36.60	59.173	1536744
	Total	32.53	56.791	2628972
1.00	1	139.68	139.616	273057
	2	175.22	149.103	384186
	Total	160.45	146.288	657243
Total	1	49.39	90.341	1365285
	2	64.32	101.597	1920930
	Total	58.12	97.357	3286215

Tests of Between-Subjects

Dependent \ GP_DAYS

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	8866623121.733[a]	3	2955541040.578	435898.013	0.000	0.285
Intercept	18275033920.185	1	18275033920.185	2695293.641	0.000	0.451
CASECONTROL	8076011536.420	1	8076011536.420	1191090.678	0.000	0.266
GNDR_CD	262162544.910	1	262162544.910	38665.047	0.000	0.012
CASECONTROL * GNDR_CD	84667754.455	1	84667754.455	12487.225	0.000	0.004
Error	22281660361.942	3286211	6780.350			
Total	42247681831.000	3286215				
Corrected Total	31148283483.675	3286214				

a. R Squared = .285 (Adjusted R Squared = .285)

Test of dependence between casecontrol and deprivation quintile

Primary care attendance

Descriptive Statistics

Dependent \ GP_DAYS

CASECONTROL		Mean	Std. Deviation	N
.00	1	36.17	57.649	614596
	2	33.71	58.853	547008
	3	31.91	55.786	550612
	4	30.30	55.478	452332
	5	29.24	55.291	464424
	Total	32.53	56.791	2628972
1.00	1	167.20	149.709	153649
	2	164.67	148.628	136752
	3	162.30	147.847	137653
	4	154.89	144.492	113083
	5	149.79	137.783	116106
	Total	160.45	146.288	657243
Total	1	62.38	99.440	768245
	2	59.90	99.663	683760
	3	57.99	97.887	688265
	4	55.22	95.506	565415
	5	53.35	92.562	580530
	Total	58.12	97.357	3286215

Tests of Between-Subjects Effects

Dependent \ GP_DAYS

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	864706874.482[a]	9	96078408.276	140318.549	0.000	0.278
Intercept	19136874621.902	1	19136874621.902	2794857.682	0.000	0.460
CASECONTROL	8436195398.448	1	8436195398.448	1232069.812	0.000	0.273
WIMD2011_5TH	40214867.966	4	10053716.991	1468.302	0.000	0.002
CASECONTROL * WIMD2011_5TH	8916405.556	4	2229101.389	325.551	0.000	0.000
Error	22501214809.194	3286205	6847.173			
Total	42247681831.000	3286215				
Corrected Total	31148283483.675	3286214				

a. R Squared = .278 (Adjusted R Squared = .278)

Test of dependence between casecontrol and age-group

Primary care attendance

Descriptive Statistics

Dependent \ GP_DAYS

CASECONTROL		Mean	Std. Deviation	N
.00	1.00	14.94	21.157	69028
	2.00	17.86	31.192	686319
	3.00	25.88	44.221	926868
	4.00	42.32	64.671	413295
	5.00	52.62	79.397	316659
	6.00	65.03	86.888	216803
	Total	32.53	56.791	2628972
1.00	1.00	41.40	45.647	12666
	2.00	93.19	99.819	166078
	3.00	144.30	133.850	240332
	4.00	207.29	149.018	112002
	5.00	250.10	162.143	80161
	6.00	250.19	163.499	46004
	Total	160.45	146.288	657243
Total	1.00	19.04	28.161	81694
	2.00	32.54	60.124	852397
	3.00	50.26	86.804	1167200
	4.00	77.50	112.208	525297
	5.00	92.51	128.948	396820
	6.00	97.44	125.931	262807
	Total	58.12	97.357	3286215

Tests of Between-Subjects Effects

Dependent \ GP_DAYS

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	11464477978.162[a]	11	1042225270.742	173999.068	0.000	0.368
Intercept	9106272365.322	1	9106272365.322	1520288.318	0.000	0.316
CASECONTROL	3696699309.027	1	3696699309.027	617162.385	0.000	0.158
AGE_GRP	2816640551.055	5	563328110.211	94047.390	0.000	0.125
CASECONTROL * AGE_GRP	1051978703.361	5	210395740.672	35125.480	0.000	0.051
Error	19683805505.514	3286203	5989.832			
Total	42247681831.000	3286215				
Corrected Total	31148283483.675	3286214				

a. R Squared = .368 (Adjusted R Squared = .368)

Test of dependence between casecontrol and gender

Opioid adverse effects

Descriptive Statistics

Dependent \ ADVERSE_EFFECTS_GP_DAYS

CASECONTROL		Mean	Std. Deviation	N
.00	1	0.11	0.555	1092228
	2	0.21	0.803	1536744
	Total	0.17	0.712	2628972
1.00	1	0.47	1.719	273057
	2	0.82	2.217	384186
	Total	0.68	2.032	657243
Total	1	0.19	0.926	1365285
	2	0.33	1.248	1920930
	Total	0.27	1.128	3286215

Tests of Between-Subjects Effects

Dependent \ ADVERSE_EFFECTS_GP_DAYS

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	159164.563[a]	3	53054.854	43342.886	0.000	0.038
Intercept	334515.170	1	334515.170	273280.421	0.000	0.077
CASECONTROL	119210.133	1	119210.133	97388.095	0.000	0.029
GNDR_CD	25404.865	1	25404.865	20754.372	0.000	0.006
CASECONTROL * GNDR_CD	7992.022	1	7992.022	6529.041	0.000	0.002
Error	4022561.974	3286211	1.224			
Total	4425240.000	3286215				
Corrected Total	4181726.537	3286214				

a. R Squared = .038 (Adjusted R Squared = .038)

Test of dependence between casecontrol and deprivation quintile

Opioid adverse effects

Descriptive Statistics

Dependent \ ADVERSE_EFFECTS_GP_DAYS

CASECONTROL		Mean	Std. Deviation	N
.00	1	0.22	0.833	614596
	2	0.18	0.684	547008
	3	0.16	0.653	550612
	4	0.15	0.652	452332
	5	0.14	0.691	464424
	Total	0.17	0.712	2628972
1.00	1	0.87	2.540	153649
	2	0.68	2.001	136752
	3	0.60	1.732	137653
	4	0.60	2.006	113083
	5	0.57	1.605	116106
	Total	0.68	2.032	657243
Total	1	0.35	1.384	768245
	2	0.28	1.103	683760
	3	0.25	0.986	688265
	4	0.24	1.085	565415
	5	0.22	0.963	580530
	Total	0.27	1.128	3286215

Tests of Between-Subjects Effects

Dependent \ ADVERSE_EFFECTS_GP_DAYS

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	144244.587[a]	9	16027.176	13044.910	0.000	0.034
Intercept	360661.645	1	360661.645	293551.306	0.000	0.082
CASECONTROL	127892.536	1	127892.536	104094.854	0.000	0.031
WIMD2011_5TH	10472.812	4	2618.203	2131.019	0.000	0.003
CASECONTROL * WIMD2011_5TH	3935.332	4	983.833	800.766	0.000	0.001
Error	4037481.950	3286205	1.229			
Total	4425240.000	3286215				
Corrected Total	4181726.537	3286214				

a. R Squared = .034 (Adjusted R Squared = .034)

Casecontrol and gender

Descriptive Statistics

Dependent \ OPDW_ATT_CNT

CASECONTROL		Mean	Std. Deviation	N
.00	1	4.20	9.735	1092228
	2	5.54	10.197	1536744
	Total	4.98	10.029	2628972
1.00	1	12.16	18.537	273057
	2	15.15	19.933	384186
	Total	13.91	19.421	657243
Total	1	5.79	12.437	1365285
	2	7.46	13.320	1920930
	Total	6.77	12.987	3286215

Tests of Between-Subjects Effects

Dependent \ OPDW_ATT_CNT

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	44463335.318[a]	3	14821111.773	95541.453	0.000	0.080
Intercept	175264293.682	1	175264293.682	1129807.642	0.000	0.256
CASECONTROL	39427551.464	1	39427551.464	254162.146	0.000	0.072
GNDR_CD	2395853.012	1	2395853.012	15444.407	0.000	0.005
CASECONTROL * GNDR_CD	348477.690	1	348477.690	2246.395	0.000	0.001
Error	509781867.691	3286211	155.128			
Total	704749016.000	3286215				
Corrected Total	554245203.010	3286214				

a. R Squared = .080 (Adjusted R Squared = .080)

Figure F.1: Example two-way ANOVA to establish interaction between factors prior to full analysis of healthcare utilisation

F.4 Mann-Whitney and Kruskall-Wallis results

F.4.1 Primary care general practice

F.4.1.1 Primary care general practice attendance by prescribing persistence

Case subjects with prescribing persistence of more than 6 months compared to those with under 6 months persistence, $p < .001$, $\eta^2 = 0.25$, $d_{Cohen} = 1.14$ (Table F.3).

F.4.1.2 Primary care general practice attendance by gender

Female case subjects compared to men $p < .001$, $\eta^2 = 0.02$, $d_{Cohen} = 0.30$.
Control group women compared to men $p < .001$, $\eta^2 = 0.01$, $d_{Cohen} = 0.22$
Women case versus control $p < .001$, $\eta^2 = 0.25$, $d_{Cohen} = 1.2$
Male cases versus control $p < .001$, $\eta^2 = 0.24$, $d_{Cohen} = 1.1$

F.4.1.3 Primary Care General Practice attendance by deprivation status

Comparison of case subjects by WIMD2011 quintile, p<.001, $\eta^2 = 0.05$, $d_{Cohen} = 0.5$. Comparison of controls by quintile, p<.001, $\eta^2 = 0.002$, $d_{Cohen} = 0.09$ which were confirmed between all quintiles by post-hoc analysis.

Table F.3: Comparison of Primary Care General Practice utilisation depending on receipt of opioid prescriptions (case versus control)

Total, mean ± standard deviation	Case	Control	p-value **(η^2, d_{Cohen})
Number of GP attendances	105 457 258	85 527 059	
Mean (SD)	160.5 (146.3)	32.53 (56.8)	<.001 (0.24, 1.13)
Median	121.0	10.0	
Prescribing persistence (cases only)			
< 6 months	67.7 (77.6)		
> 6 months	198.8 (150.8)		<.001 (0.25, 1.14)
Gender			
Female	175.2 (149.1)	36.6 (59.2)	<.001 (0.25, 1.2)
Male	139.7 (139.6)	26.8 (52.7)	<.001 (0.24, 1.1)
Deprivation quintile*			
WIMD1	167.2 (149.7)	36.2 (57.7)	<.001 (0.23, 1.1)
WIMD2	164.7 (148.6)	33.7 (58.9)	<.001 (0.24, 1.1)
WIMD3	162.3 (147.5)	31.9 (55.8)	<.001 (0.25, 1.2)
WIMD4	154.9 (144.5)	30.3 (55.5)	<.001 (0.25, 1.2)
WIMD5	149.8 (137.8)	29.2 (55.3)	<.001 (0.26, 1.2)
Age group (years)			
18 – 24	41.4 (45.7)	14.9 (21.2)	<.001 (0.09, 0.6)
25 – 44	93.2 (99.8)	17.9 (31.2)	<.001 (0.24, 1.1)
45 – 64	144.3 (133.9)	25.9 (44.2)	<.001 (0.27, 1.2)
65 – 74	207.3 (149.0)	42.3 (64.7)	<.001 (0.30, 1.3)
75 – 84	250.1 (162.1)	52.6 (79.4)	<.001 (0.30, 1.3)
≥ 85	250.2 (163.5)	65.0 (86.9)	<.001 (0.23, 1.1)
GP visits for ADEs possibly associated with opioids	444 050	450 510	
Mean ± SD	0.68 (2.0)	0.17 (0.7)	<.001 (0.02, 0.28)
Gender			
Female	0.82 (2.2)	0.21 (0.8)	<.001 (0.03, 0.33)
Male	0.47 (1.7)	0.11 (0.6)	<.001 (0.01, 0.21)
Deprivation quintile*			
WIMD1	0.87 (2.5)	0.22 (0.8)	<.001 (0.03, 0.3)
WIMD2	0.68 (2.0)	0.18 (0.7)	<.001 (0.02, 0.3)
WIMD3	0.60 (1.7)	0.16 (0.7)	<.001 (0.02, 0.3)
WIMD4	0.6 (2.0)	0.15 (0.7)	<.001 (0.02, 0.25)
WIMD5	0.57 (1.6)	0.14 (0.7)	<.001 (0.02, 0.26)
All tests and referrals from primary care	206 747	158 290	
Mean ± SD	0.31 (0.9)	0.06 (0.3)	<.001 (0.01, 0.21)
Recorded imaging (X-ray, CT, MRI etc.)	90 700	74 756	
Mean ± SD	0.14 (0.5)	0.03 (0.2)	<.001 (0.003, 0.10)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant

F.4.1.4 Primary care General Practice attendance by age-group

Pairwise comparisons of the six age-groups of case subjects, p<.001, $\eta^2 = 0.19$, $d_{Cohen} = 0.97$, other than for the two oldest groups (75-84 years and 85+ years, p>0.05).

Differences between the mean attendances of all control subject age-groups p<.001, $\eta^2 = 0.03$, $d_{Cohen} = 0.32$. Differences in attendance were confirmed between all age-groups when compared pairwise (p<.001).

F.4.1.5 Tests and imaging from Primary Care

Case subjects versus controls for tests, p<.001, $\eta^2 = 0.01$, $d_{Cohen} = 0.21$ and imaging appointments, p<.001, $\eta^2 = 0.003$, $d_{Cohen} = 0.1$)

F.4.2 Out-Patient attendance

Cases versus control, p<.001, $\eta^2 = 0.09$, $d_{Cohen} = 0.63$.

F.4.2.1 Out-patient attendance by prescribing persistence

Case subjects with a prescribing persistence of more than 6 months compared to under 6 months, p<.001, $\eta^2 = 0.16$, $d_{Cohen} = 0.88$.

F.4.2.2 Out-patient attendance by gender

Case subject women compared to men, p<.001, $\eta^2 = 0.01$, $d_{Cohen} = 0.24$.
Control women compared to men, p<.001, $\eta^2 = 0.01$, $d_{Cohen} = 0.22$.

Table F.4: Comparison of out-patient resource utilisation depending on receipt of opioid prescriptions (case versus control)

Total, mean ± standard deviation	Case	Control	p-value** (η^2, d_{Cohen})
Number of Outpatient attendances	9 140 922	13 098 410	
Mean ± SD	13.9 (19.4)	5.0 (10.0)	<.001 (0.09, 0.63)
Prescribing persistence (cases only)			
< 6 months	5.6 (10.1)		
> 6 months	17.4 (21.2)		<.001 (0.16, 0.88)
Gender			
Female	15.2 (19.9)	5.5 (10.2)	<.001 (0.10, 0.65)
Male	12.2 (18.5)	4.2 (9.7)	<.001 (0.09, 0.62)
Deprivation quintile*			
WIMD1	○ (20.7)	5.3 (10.0)	<.001 (0.09, 0.64)
WIMD2	14.4 (19.9)	5.1 (10.4)	<.001 (0.09, 0.64)
WIMD3	13.5 (19.0)	5.0 (9.7)	<.001 (0.09. 0.62)
WIMD4	13.0 (18.4)	4.6 (9.3)	<.001 (0.09, 0.63)
WIMD5	13.0 (18.4)	4.8 (10.7)	<0001 (0.09, 0.64)
Age group (years)			
18 – 24	4.6 (8.1)	1.7 (5.7)	<.001 (0.06, 0.48)
25 – 44	9.9 (15.0)	3.4 (7.3)	<.001 (0.09, 0.61)
45 – 64	12.7 (18.7)	4.3 (9.0)	<.001 (0.10, 0.66)
65 – 74	17.2 (21.9)	7.3 (12.9)	<.001 (0.09, 0.63)
75 – 84	20.7 (23.3)	7.9 (12.9)	<.001 (0.11, 0.70)
≥ 85	17.4 (20.5)	5.7 (9.8)	<.001 (0.11, 0.70)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant

F.4.2.3 Out-patient attendance by deprivation

Case subject differences in attendance by quintile, p<.001, $\eta^2 = .002$, $d_{Cohen} = 0.10$. Post-hoc analysis confirmed those differences in all but WIMD4 and WIMD5 quintiles (p>.5) when attendance was directly compared.
Control group differences in attendance by deprivation quintile, p<.001, $\eta^2 = .002$, $d_{Cohen} = .09$, which was confirmed by pairwise comparisons.

F.4.2.4 Out-patient attendance by age-group

Case subject comparisons of out-patient attendances between all age-groups, $p<.001$, $\eta^2 = .062$, $d_{Cohen} = .51$ and were confirmed by pairwise comparisons. Control subject comparisons, $p<.001$, $\eta^2 = .055$, $d_{Cohen} = .48$ and again, confirmed by pairwise comparison.

F.4.3 Emergency Department Utilisation

Case subjects versus control subjects, $p<.001$, $\eta^2 = 0.07$, $d_{Cohen} = .53$.

F.4.3.1 Emergency department attendance by prescription persistence

Case subjects receiving opioid prescriptions for more than 6 months compared to shorter durations of prescribing (Table F.5).

F.4.3.2 Emergency department attendance by gender

Male versus female case subjects, $p<.001$, $\eta^2 = 0$, $d_{Cohen} = .004$.
Female versus male controls, $p<.001$, $\eta^2 = 0$, $d_{Cohen} = .004$.

Table F.5: Comparison of Emergency department resource utilisation depending on receipt of opioid prescriptions (case versus control)

Total, mean (standard deviation)	Case	Control	p-value** (η^2, d_{Cohen})
Number of Emergency Department attendances	1 243 641 1.89 (3.4)	1 566 627 0.6 (1.8)	<.001 (0.07, 0.53)
Prescribing persistence (cases only)			
< 6 months	0.96 (1.9)		<.001 (0.06, 0.51)
> 6 months	2.3 (3.8)		
Gender			
Female	1.9 (3.4)	0.58 (1.7)	<.001 (0.06, 0.52)
Male	1.9 (3.4)	0.61 (1.8)	<.001 (0.07, 0.53)
Deprivation quintile*			
WIMD1	2.3 (3.9)	0.77 ± 2.1	<.001 (0.08, 0.57)
WIMD2	2.4 (3.8)	0.65 ± 1.7	<.001 (0.07, 0.55)
WIMD3	1.8 (3.2)	0.55 ± 1.9	<.001 (0.07, 0.53)
WIMD4	1.64 ± 2.9	0.53 ± 1.4	<.001 (0.05, 0.47)
WIMD5	1.5 ± 2.6	0.41 ± 1.2	<.001 (0.06, 0.52)
Age group (years)			
18 – 24	2.0 ± 3.9	0.86 ± 2.2	<.001 (0.03, 0.37)
25 – 44	2.2 ± 3.8	0.61 ± 1.5	<.001 (0.08, 0.59)
45 – 64	1.7 ± 3.2	0.56 ± 1.7	<.001 (0.06, 0.48)
65 – 74	1.5 ± 3.1	0.56 ± 2.2	<.001 (0.05, 0.47)
75 – 84	2.0 ± 3.1	0.58 ± 1.6	<.001 (0.08, 0.59)
≥ 85	2.5 (3.3)	0.67 (1.6)	<.001 (0.10, 0.66)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant

F.4.3.3 Emergency Department attendance by deprivation

Case subject differences between quintiles, $p<.001$, $\eta^2 = 0.01$, $d_{Cohen} = 0.20$.
Control group differences by quintile, $p<.001$, $\eta^2 = 0.005$, $d_{Cohen} = 0.14$.

Differences in attendance numbers were significant between all quintiles when compared in pairs. Case subjects versus controls in WIMD1 quintiles, p<.001, η^2 = 0.08, d_{Cohen} = 0.57 (Table F.5).
Cases compared to controls in WIMD5 quintile, p<.001, η^2 = 0.06, d_{Cohen} = 0.52.

F.4.3.4 Emergency Department attendance by age-group

Comparisons of mean attendances in case subjects by age-group (p<.001, η^2 = 0.02, d_{Cohen} = 0.24).

Control group by age-group, p<.001, η^2 = 0.002, d_{Cohen} = 0.09. Pairwise comparison confirmed differences between age groups other than the 45 – 64 and ≥ 85 years groups where a statistical difference was not found (p > 0.1).

F.4.4 Inpatient attendance

F.4.4.1 In-Patient attendance and length of stay

Case subjects versus controls, p<.001, η^2 = 0.07, d_{Cohen} = 0.53.
Length of stay case versus controls, p<.001, η^2 = 0.02, d_{Cohen} = 0.28.

F.4.4.2 In-patient utilisation by prescription persistence

Case subjects with >6 months prescription persistence (Table F.6) compared to under 6 months use, p<.001, η^2 = 0.005, d_{Cohen} = 0.47.

F.4.4.3 In-patient utilisation by gender

In-patient admissions, female case subjects compared to male cases, p<.001, η^2 = 0.02, d_{Cohen} = 0.26.
Length of stay female case subjects versus male cases, p<.001, η^2 = 0.012, d_{Cohen} = 0.22 (Table F.6).
Control subjects, in-patient admissions for females compared to male, p<.001, η^2 = 0.01, d_{Cohen} = 0.18.
Female controls length of stay versus men, p<.001, η^2 = 0.06, d_{Cohen} = 0.16.
Female controls compared to female case subjects' length of stay, p < .001, η^2 = 0.02, D_{Cohen} = 0.29, (Table F.6).
Male controls versus male case subjects' length of stay, p <.001, η^2 = 0.02, D_{Cohen} = 0.27.

Table F.6: Comparison of In-patient admission and length of stay depending on receipt of opioid prescriptions (case versus control)

Total, mean (standard deviation)	Case	Control	p-value** (η^2, d_{Cohen})
Number of In-patient admissions	3 021 645	5 676 577	
Mean ± SD	4.6 (8.5)	2.2 (6.3)	<.001 (0.07, 0.53)
Prescribing persistence (cases only)	2.9 (6.2)		
< 6 months	5.3 (9.2)		<.001 (0.05, 0.47)
> 6 months			
Gender			
Female	5.0 (8.1)	2.3 (6.0)	<.001 (0.07, 0.56)
Male	4.1 (9.0)	2.0 (6.7)	<.001 (0.06, 0.51)
Deprivation quintile			
WIMD1	4.9 (8.1)	2.3 (4.8)	<.001 (0.07, 0.53)
WIMD2	4.8 (8.7)	2.2 (4.7)	<.001 (0.07, 0.55)

	WIMD3	4.5 (8.3)	2.3 (8.3)	<.001 (0.06, 0.51)
	WIMD4	4.4 (9.0)	2.0 (6.4)	<.001 (0.07, 0.55)
	WIMD5	4.2 (8.3)	1.9 (6.9)	<.001 (0.07, 0.54)
Age group (years)				
	18 – 24	3.5 (6.5)	0.5 (2.1)	<.001 (0.13, 0.76)
	25 – 44	3.9 (7.4)	1.0 (2.7)	<.001 (0.12, 0.74)
	45 – 64	3.5 (7.8)	1.2 (4.8)	<.001 (0.09, 0.64)
	65 – 74	5.0 (9.3)	3.1 (10.0)	<.001 (0.05, 0.47)
	75 – 84	6.9 (10.1)	4.6 (6.0)	<.001 (0.02, 0.29)
	≥ 85	8.3 (8.6)	5.1 (9.3)	<.001 (0.04, 0.39)
Length of stay (days)		10 758 522	45 482 557	
	Mean ± SD	16.4 (54.7)	17.3 (64.9)	<.001 (0.02, 0.28)
Prescribing persistence (cases only)		10.4 (46.7)		
	< 6 months	18.8 (57.5)		<.001 (0.03, 0.37)
	> 6 months			
Gender				
	Female	18.0 (57.0)	19.3 (68.2)	<.001 (0.02, 0.29)
	Male	14.1 (51.3)	14.5 (60.0)	<.001 (0.02, 0.27)
Deprivation quintile				
	WIMD1	17.6 (58.6)	17.9 (65.8)	<.001 (0.02, 0.28)
	WIMD2	16.9 (56.4)	18.0 (72.9)	<.001 (0.02, 0.31)
	WIMD3	16.5 (53.6)	18.9 (62.1)	<.001 (0.02, 0.27)
	WIMD4	15.0 (49.6)	15.1 (55.8)	<.001 (0.02, 0.30)
	WIMD5	15.3 (53.4)	15.9 (65.4)	<.001 (0.02, 0.26)
Age group (years)				
	18 – 24	5.1 (22.4)	0.8 (7.0)	<.001 (0.08, 0.58)
	25 – 44	6.8 (33.4)	1.8 (21.1)	<.001 (0.07, 0.57)
	45 – 64	8.1 (40.0)	5.0 (37.7)	<.001 (0.04, 0.41)
	65 – 74	15.5 (50.9)	20.5 (66.9)	<.001 (0.01, 0.20)
	75 – 84	34.6 (78.8)	50.3 (108.2)	<.001 (0.002, 0.10)
	≥ 85	67.7 (96.0)	70.3 (110.1)	<.001 (.001, 0.05)

*Deprivation quintile based on Welsh Index of Multiple Deprivation 2011. WIMD1 =most deprived, WIMD5 = least deprived **p-value <0.05 = significant

F.4.4.4 In-patient utilisation by deprivation

Case subjects mean average number of admissions by deprivation quintile, $p < .001$, $\eta^2 = 0.002$, $D_{Cohen} = 0.09$, confirmed by pairwise comparison.
Length of in-patient stay for case subjects by deprivation quintile and confirmed by pairwise comparisons, $p < .001$, $\eta^2 = 0.002$, $D_{Cohen} = 0.08$.
Control group admissions by deprivation, $p < .001$, $\eta^2 = 0.002$, $D_{Cohen} = 0.08$.
Length of stay for control group by deprivation quintile (WIMD3) (Table F.6) and confirmed by pairwise comparisons, $p < .001$, $\eta^2 = .001$, $D_{Cohen} = 0.08$)

F.4.4.5 In-patient utilisation by age-group

Average in-patient admissions between case-subject control groups was found to be statistically significant, $p < .001$, $\eta^2 = 0.08$, $D_{Cohen} = 0.59$. There was no difference in the number of admissions for age-groups 18-24 years and 45-64 years.
Case subject length of stay compared between and within age-groups, $p < .001$, $\eta^2 = 0.13$, $D_{Cohen} = 0.77$.
Differences between age-group ranked admissions for cases versus controls were statistically significant and confirmed by direct pairwise comparisons, $p < .001$, $\eta^2 = 0.22$, $D_{Cohen} = 1.05$.

Control group differences in average length of stay by age-group, $p < .001$, $\eta^2 = 0.30$, $D_{Cohen} = 1.30$ and confirmed by pairwise comparison.
Case versus control subjects aged 18-24 years number of admissions, $p < .001$, $\eta^2 = 0.13$, $D_{Cohen} = 0.76$ and admission duration, $p < .001$, $\eta^2 = 0.08$, $D_{Cohen} = 0.58$.
Age-group 75-84 control subjects versus controls, $p < .001$, $\eta^2 = 0.02$, $D_{Cohen} = 0.29$. Average length of stay, $p < .001$, $\eta^2 = 0.002$, $D_{Cohen} = 0.10$.

F.5 Example of outpatient unit costs for cost-analysis

Table F.7: Example calculation for weighting unit costs using National Unit costs for Emergency Department attendance in 2015

National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts - Emergency Medicine									
Service Code	**Service Description**	**Currency Code**	**Currency Description**	**Attendances**	**National Average Unit Cost**	**Lower Quartile Unit Cost**	**Upper Quartile Unit Cost**	**No. Data Submissions**	**Number of attendances*National average unit cost**
T01A	Type 01 Admitted	VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	29,523	£417	£253	£560	133	£12,314,719.19
T01A	Type 01 Admitted	VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment	141,663	£371	£270	£460	136	£52,537,385.33
T01A	Type 01 Admitted	VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	327,342	£278	£221	£330	139	£91,026,130.78
T01A	Type 01 Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	787,182	£247	£198	£281	138	£194,285,369.36
T01A	Type 01 Admitted	VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	193,707	£221	£174	£248	139	£42,800,957.00
T01A	Type 01 Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	106,822	£161	£127	£192	139	£17,249,530.88
T01A	Type 01 Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	525,452	£201	£158	£225	139	£105,547,785.39
T01A	Type 01 Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	1,255,603	£184	£150	£213	140	£231,129,209.84
T01A	Type 01 Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	483,365	£133	£101	£146	140	£64,167,368.34
T01A	Type 01 Admitted	VB10Z	Emergency Medicine, Dental Care	9,132	£72	£67	£67	21	£657,584.86
T01A	Type 01 Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	190,837	£109	£77	£132	138	£20,885,973.36
T01A	Type 01 Admitted	VB99Z	Emergency Medicine, Patient Dead On Arrival	73	£155	£75	£251	22	£11,320.66
T01NA	Type 01 Non-Admitted	VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	13,581	£373	£187	£526	133	£5,060,904.71
T01NA	Type 01 Non-Admitted	VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment	42,274	£343	£270	£395	134	£14,520,781.52
T01NA	Type 01 Non-Admitted	VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	273,027	£249	£205	£292	137	£68,103,569.13
T01NA	Type 01 Non-Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	294,431	£224	£186	£240	135	£65,878,121.46
T01NA	Type 01 Non-Admitted	VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	203,529	£187	£158	£210	135	£38,001,656.59
T01NA	Type 01 Non-Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	347,157	£132	£108	£147	136	£45,958,183.51
T01NA	Type 01 Non-Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	1,339,334	£162	£142	£181	136	£217,506,975.45
T01NA	Type 01 Non-Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	2,815,693	£151	£134	£165	137	£426,326,017.19
T01NA	Type 01 Non-Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	3,416,947	£107	£88	£122	138	£366,452,455.00
T01NA	Type 01 Non-Admitted	VB10Z	Emergency Medicine, Dental Care	25,967	£111	£113	£113	65	£2,894,520.37
T01NA	Type 01 Non-Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	1,864,147	£89	£67	£106	136	£165,450,349.47
T01NA	Type 01 Non-Admitted	VB99Z	Emergency Medicine, Patient Dead On Arrival	579	£279	£55	£251	38	£161,300.09

T02A	Type 02 Admitted	VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	19	£144	£108	£164	7	£2,728.05
T02A	Type 02 Admitted	VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment	32	£316	£307	£392	5	£10,099.62
T02A	Type 02 Admitted	VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	327	£195	£122	£253	17	£63,799.36
T02A	Type 02 Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	328	£276	£299	£299	9	£90,465.95
T02A	Type 02 Admitted	VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	270	£242	£230	£293	7	£65,268.68
T02A	Type 02 Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	553	£130	£123	£123	13	£72,009.16
T02A	Type 02 Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	3,359	£152	£138	£138	9	£509,621.16
T02A	Type 02 Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	7,933	£146	£143	£143	16	£1,156,635.78
T02A	Type 02 Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	32,885	£89	£89	£89	19	£2,933,940.38
T02A	Type 02 Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	4,182	£96	£96	£96	17	£401,160.73
T02A	Type 02 Admitted	VB99Z	Emergency Medicine, Patient Dead On Arrival	1	£8,724	£8,724	£8,724	1	£8,724.32
T02NA	Type 02 Non-Admitted	VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	752	£120	£86	£142	13	£89,899.99
T02NA	Type 02 Non-Admitted	VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment	49	£257	£152	£339	9	£12,602.94
T02NA	Type 02 Non-Admitted	VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	9,511	£182	£102	£253	18	£1,733,939.90
T02NA	Type 02 Non-Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	229	£179	£121	£188	14	£40,989.48
T02NA	Type 02 Non-Admitted	VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	3,217	£93	£70	£85	17	£298,756.74
T02NA	Type 02 Non-Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	12,891	£82	£46	£98	18	£1,054,086.73
T02NA	Type 02 Non-Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	4,076	£148	£146	£146	15	£601,924.39
T02NA	Type 02 Non-Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	62,374	£108	£42	£135	19	£6,713,672.35
T02NA	Type 02 Non-Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	228,094	£83	£51	£95	20	£19,018,553.63
T02NA	Type 02 Non-Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	148,397	£85	£51	£128	21	£12,685,150.12
T03A	Type 03 Admitted	VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	20	£182	£110	£140	9	£3,632.81
T03A	Type 03 Admitted	VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment	208	£248	£229	£229	7	£51,591.54
T03A	Type 03 Admitted	VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	689	£212	£177	£177	16	£146,384.71
T03A	Type 03 Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	2,333	£141	£110	£119	18	£328,200.34
T03A	Type 03 Admitted	VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	1,203	£118	£95	£112	19	£142,473.11
T03A	Type 03 Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	7,988	£53	£43	£59	23	£424,476.94
T03A	Type 03 Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	5,755	£84	£52	£117	26	£483,199.76
T03A	Type 03 Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	29,034	£58	£36	£67	30	£1,685,513.68
T03A	Type 03 Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	74,874	£58	£43	£87	31	£4,329,419.72

T03A	Type 03 Admitted	VB10Z	Emergency Medicine, Dental Care	7	£53	£38	£43	3	£371.28
T03A	Type 03 Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	270,185	£58	£59	£59	33	£15,610,126.72
T03NA	Type 03 Non-Admitted	VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	96	£194	£105	£204	20	£18,595.80
T03NA	Type 03 Non-Admitted	VB02Z	Emergency Medicine, Category 3 Investigation with Category 4 Treatment	162	£326	£204	£398	18	£52,844.98
T03NA	Type 03 Non-Admitted	VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	22,616	£89	£78	£78	28	£2,015,702.24
T03NA	Type 03 Non-Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	37,396	£84	£70	£70	44	£3,149,254.26
T03NA	Type 03 Non-Admitted	VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	85,397	£70	£62	£62	44	£5,966,785.48
T03NA	Type 03 Non-Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	69,579	£79	£39	£105	46	£5,513,453.59
T03NA	Type 03 Non-Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	86,777	£120	£98	£138	44	£10,392,250.12
T03NA	Type 03 Non-Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	203,695	£96	£73	£116	48	£19,482,590.16
T03NA	Type 03 Non-Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	786,022	£62	£50	£75	54	£49,076,037.60
T03NA	Type 03 Non-Admitted	VB10Z	Emergency Medicine, Dental Care	15,418	£94	£94	£94	8	£1,442,145.51
T03NA	Type 03 Non-Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	777,592	£56	£44	£68	53	£43,679,369.98
T03NA	Type 03 Non-Admitted	VB99Z	Emergency Medicine, Patient Dead On Arrival	815	£65	£64	£64	4	£52,905.59
T04A	Type 04 Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	1,731	£246	£246	£246	1	£425,254.77
T04A	Type 04 Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	46	£55	£55	£55	1	£2,507.00
T04A	Type 04 Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	5	£47	£47	£47	1	£233.60
T04A	Type 04 Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	60	£39	£39	£39	1	£2,335.80
T04A	Type 04 Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	1,316	£31	£31	£31	1	£40,980.24
T04A	Type 04 Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	1,436	£16	£16	£16	1	£22,358.52
T04NA	Type 04 Non-Admitted	VB01Z	Emergency Medicine, Any Investigation with Category 5 Treatment	67,532	£45	£44	£45	4	£3,015,356.74
T04NA	Type 04 Non-Admitted	VB03Z	Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment	146,929	£38	£32	£43	6	£5,597,201.96
T04NA	Type 04 Non-Admitted	VB04Z	Emergency Medicine, Category 2 Investigation with Category 4 Treatment	2	£70	£70	£70	1	£140.14
T04NA	Type 04 Non-Admitted	VB05Z	Emergency Medicine, Category 2 Investigation with Category 3 Treatment	707	£67	£53	£81	4	£47,519.29
T04NA	Type 04 Non-Admitted	VB06Z	Emergency Medicine, Category 1 Investigation with Category 3-4 Treatment	79,931	£37	£36	£36	6	£2,946,388.46
T04NA	Type 04 Non-Admitted	VB07Z	Emergency Medicine, Category 2 Investigation with Category 2 Treatment	208,614	£42	£38	£38	6	£8,861,370.44
T04NA	Type 04 Non-Admitted	VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment	14,265	£66	£70	£70	6	£934,834.48
T04NA	Type 04 Non-Admitted	VB09Z	Emergency Medicine, Category 1 Investigation with Category 1-2 Treatment	259,559	£55	£38	£70	8	£14,378,321.34
T04NA	Type 04 Non-Admitted	VB10Z	Emergency Medicine, Dental Care	6	£38	£36	£41	2	£227.46
T04NA	Type 04 Non-Admitted	VB11Z	Emergency Medicine, No Investigation with No Significant Treatment	640,171	£37	£34	£41	15	£23,769,564.90
T04NA	Type 04 Non-Admitted	VB99Z	Emergency Medicine, Patient Dead On Arrival	4	£262	£262	£262	1	£1,049.28

			Summed total attendances	**19,107,021**				**Total**	**£2,520,585,169.28**
							Weighted cost = Total costs/Total attendances		**£131.92**

F.6 Threshold analysis

Table F.8: Output of threshold analysis for healthcare services costs using changes in case subject costs. p-values attained from Mann-Whitney analysis case versus control subjects.

	Mean average costs (£) (standard error of the mean)			
% of case subjects' costs	**Cases** (n = 657 243)	**Controls** (n = 2 628 972)	**Difference (95% CI)**	**p-value*** (d)
Total Primary care				
15	829.62 (0.93)	1121.34 (1.21)	-291.73 (-294.72 - -288.74)	<0.001 (-0.26)
20	1106.15 (1.24)		-15.19 (-18.60 - -11.79)	<0.001 (-0.01)
20.2	1117.22 (1.26)		-4.13 (-7.54 - -0.71)	<0.05 (-0.003)
20.3	1122.75 (1.26)		1.40 (-2.02 – 4.83)	0.422 (0.001)
20.4	1128.28 (1.27)		6.93 (3.50 – 10.37)	<0.001 (0.01)
21	1161.46 (1.31)		40.12 (36.63 – 43.60)	<0.001 (0.03)
22	1216.77 (1.37)		95.43 (91.85 – 99.00)	<0.001 (0.07)
23	1272.08 (1.43)		150.73 (147.06 – 154.40)	<0.001 (0.11)
25	1382.69 (1.56)		261.35 (257.49 – 265.21)	<0.001 (0.18)
Total Secondary Care				
80	7314.02 (23.40)	8009.06 (16.27)	-695.04 (-750.89 - -639.18)	<0.001 (0.03)
86	7862.58 (25.15)		-146.48 (-205.20 - -87.77)	<0.001 (0.01)
87	7954.00 (25.44)		-55.06 (-114.25 – 4.14)	0.068 (-0.003)
87.5	7999.71 (25.59)		-9.35 (-68.78 – 50.09)	0.758 (0.00)
88	8045.43 (25.74)		36.37 (-23.31 -96.05)	0.232 (0.002)
88.5	8091.14 (25.88)		82.08 (22.16 – 142.00)	<0.05 (0.004)
90	8228.28 (26.32)		219.22 (158.57 – 279.87)	<0.001 (0.01)
92	8411.13 (26.91)		402.07 (340.44 – 463.70)	<0.001 (0.02)
95	8685.40 (27.78)		676.34 (613.24 – 739.45)	<0.001 (0.03)

Total costs					
	50	8226.68 (16.54)	9757.27 (16.77)	-1530.60 (-1576.76 - -1484.44)	<0.001 (-0.09)
	55	9049.34 (18.19)		-707.93 (-756.42 - -659.44)	<0.001 (-0.04)
	58	9542.94 (19.19)		-214.33 (-264.27 - -164.39)	<0.001 (-0.01)
	58.5	9625.21 (19.35)		-132.06 (-182.25 - -81.88)	<0.001 (-0.01)
	59	9707.48 (19.52)		-49.79 (-100.22 - -0.64)	0.053 (-0.003)
	59.5	9789.74 (19.68)		32.47 (-18.20 – 83.15)	0.209 (0.002)
	60	9872.01 (19.85)		114.74 (63.82 – 165-66)	<0.001 (0.01)
	65	10694.68 (21.50)		937.41 (883.97 – 990.85)	<0.001 (0.05)
	70	11517.35 (23.16)		1760.08 (1704.04 – 1816.11)	<0.001 (0.09)

*p-value calculated from t-test (case-control), <0.05 = significant

Holm-Bonferroni confirmed it was correct to reject the null hypothesis

Appendix G Prescribing Persistence

G.1 Descriptive annual data for prescribing persistence

Table G.1: Annualised prescribing persistence data, full breakdown

Year	2005		2006		2007		2008		2009		2010	
Number of events	440975		307205		322266		335182		346194		361054	
Mean prescription duration days	3.38		5.60		5.69		6.71		7.56		8.13	
(SD)	20.922		33.522		35.176		42.892		47.033		51.040	
Mean age (SD)	57.25 (17.78)		56.02 18.236		55.71 18.198		55.62 18.112		55.55 18.168		55.80 18.042	
Sex												
Male	168112	38.1	121009	39.4	130138	40.4	136633	40.8	143032	41.3	149130	41.3
Female	272863	61.9	186196	60.6	192128	59.6	198549	59.2	203162	58.7	211924	58.7
First opioid in prescription period												
	10012	2.3	7219	2.3	8113	2.5	9095	2.7	10386	3.0	12331	3.4
Strong	430963	97.7	299986	97.7	314153	97.5	326087	97.3	335808	97.0	348723	96.6
Weak												
Health Board												
ABMUHB	120916	27.4	85310	27.8	88471	27.5	91171	27.2	93782	27.1	95796	26.5
ABUHB	75711	17.2	52521	17.1	55599	17.3	57575	17.2	59273	17.1	63424	17.6
BCUHB	78341	17.8	55042	17.9	59418	18.4	62567	18.7	65943	19.0	69641	19.3
CVUHB	61890	14.0	43509	14.2	45207	14.0	47355	14.1	48626	14.0	50191	13.9
CTUHB	51051	11.6	34059	11.1	34852	10.8	35872	10.7	36319	10.5	37662	10.4
HDUHB	43669	9.9	29805	9.7	31108	9.7	32557	9.7	33699	9.7	35517	9.8
PTHB	9397	2.1	6959	2.3	7611	2.4	8085	2.4	8552	2.5	8823	2.4
Deprivation quintile at first prescription in period												
WIMD1	119414	28.1	80970	27.3	83444	26.9	86559	26.9	88320	26.5	92146	26.6
WIMD2	95924	22.6	66335	22.4	68743	22.2	71004	22.0	73418	22.0	77165	22.3
WIMD3	85544	20.2	60120	20.3	63098	20.3	65760	20.4	67601	20.3	70625	20.4
WIMD4	62389	14.7	44529	15.0	47640	15.4	49933	15.5	52152	15.7	54439	15.7
WIMD5	61049	14.4	44310	15.0	47268	15.2	48889	15.2	51544	15.5	52324	15.1
	424320	100.0	296264	100.0	310193	100.0	322145	100.0	333035	100.0	346699	100.0
Recorded diagnosis												
Big six non cancer pain	305263	69.2	216685	70.5	228281	70.8	239400	71.4	249382	72.0	261686	72.5
Depression/anxiety	112283	25.5	80930	26.3	86196	26.7	91723	27.4	97031	28.0	103404	28.6
Buprenorphine	1511		1821		2642		3817		4749		6032	

Codeine	248193	194023	208489	219476	226958	236636
Dextropropoxyphene	40037	4272	1684	883	685	606
Dihydrocodeine	95674	63929	62160	59877	57822	55898
Fentanyl	1980	1723	1992	2354	2608	2866
Morphine	4489	2994	3416	3924	4336	5398
Oxycodone	1248	903	1166	1417	2029	2556
Tapentadol						
Tramadol	46491	36672	39929	42739	46348	50443
Other	1352	868	788	695	659	619

Year	**2011**		**2012**		**2013**		**2014**		**2015**	
Number of events	377112		397104		412010		449169		559762	
Mean prescription duration days	8.50		9.51		9.71		9.96		15.61	
(SD)	53.460		61.351		61.639		65.529		118.737	
Mean age (SD)	55.76 18.001		55.88 17.928		56.10 17.848		56.36 17.708		56.78 17.388	
Sex										
Male	156156	41.4	164291	41.4	169455	41.1	184564	41.1	228299	40.8
Female	220956	58.6	232813	58.6	242555	58.9	264605	58.9	331463	59.2
First opioid in prescription period										
	14163	3.8	17171	4.3	21558	5.2	27323	6.1	38340	6.8
Strong	362949	96.2	379933	95.7	390452	94.8	421846	93.9	521422	93.2
Weak										
Health Board										
ABMUHB	99530	26.4	102392	25.8	104214	25.3	111294	24.8	141094	25.2
ABUHB	65956	17.5	69934	17.6	71937	17.5	77934	17.4	96513	17.2
BCUHB	73881	19.6	80452	20.3	88452	21.5	99911	22.2	123183	22.0
CVUHB	52052	13.8	55508	14.0	56909	13.8	61713	13.7	76817	13.7
CTUHB	39036	10.4	40734	10.3	41403	10.0	45034	10.0	55711	10.0
HDUHB	36779	9.8	37898	9.5	38006	9.2	41545	9.2	52499	9.4
PTHB	9878	2.6	10186	2.6	11089	2.7	11738	2.6	13945	2.5
Deprivation quintile at first prescription in period										
WIMD1	95575	26.4	101238	26.6	105037	26.5	114978	26.7	143403	26.8
WIMD2	81013	22.4	85608	22.5	88023	22.2	95370	22.1	118945	22.2
WIMD3	74003	20.4	76846	20.2	80709	20.4	88895	20.6	110162	20.6
WIMD4	56965	15.7	59884	15.7	62349	15.8	67517	15.7	83403	15.6
WIMD5	54539	15.1	57729	15.1	59594	15.1	64026	14.9	79883	14.9
	362095	100.0	381305	100.0	395712	100.0	430786	100.0	535796	100.0

Recorded diagnosis										
Big six non cancer pain	275129	73.0	291646	73.4	303601	73.7	332683	74.1	418741	74.8
Depression/anxiety	109881	29.1	118635	29.9	125358	30.4	138841	30.9	174963	31.3
Buprenorphine	6870		7413		7966		8620		10135	
Codeine	247418		260215		268130		297982		379209	
Dextropropoxyphene	466		402		281		307		343	
Dihydrocodeine	54249		52528		52427		52869		62892	
Fentanyl	3025		3292		3720		3949		4454	
Morphine	6720		8909		12822		17788		26462	
Oxycodone	2925		3436		3363		3755		5008	
Tapentadol	31		114		195		373		716	
Tramadol	54874		60290		62631		63099		70031	
Other	534		505		475		427		512	

G.1.1 Annual descriptive data for prescribing persistence greater than 31 days

Table G.2: Descriptive data with all single, not repeated within 31-day events removed

Year	**2005**		**2006**		**2007**		**2008**		**2009**		**2010**	
Number of events	22722		21331		23900		27490		31292		34415	
Mean prescription duration days	65.58		80.64		76.75		81.79		83.61		85.35	
(SD)	66.452		100.665		105.975		127.634		134.592		144.018	
Mean age (SD)	61.53 17.565		59.63 16.837		58.69 16.883		58.02 16.720		57.76 16.720		57.68 16.551	
Sex												
Male	8881	39.1	8420	39.5	9754	40.8	11545	42.0	13543	43.3	14955	43.5
Female	13841	60.9	12911	60.5	14146	59.2	15945	58.0	17749	56.7	19460	56.5
First opioid in prescription												
period	1253	5.5	606	2.8	705	2.9	854	3.1	1156	3.7	1405	4.1
Strong	21469	94.5	20725	97.2	23195	97.1	26636	96.9	30136	96.3	33010	95.9
Weak												
Health Board												
ABMUHB	13797	60.7	13722	64.3	14365	60.1	15451	56.2	16816	53.7	17507	50.9
ABUHB	2058	9.1	1764	8.3	2162	9.0	2614	9.5	3096	9.9	3658	10.6
BCUHB	1690	7.4	1487	7.0	2040	8.5	2748	10.0	3548	11.3	4238	12.3
CVUHB	1454	6.4	1159	5.4	1560	6.5	1949	7.1	2380	7.6	2740	8.0
CTUHB	1443	6.4	1161	5.4	1265	5.3	1573	5.7	1857	5.9	2111	6.1
HDUHB	1673	7.4	1348	6.3	1658	6.9	2081	7.6	2429	7.8	2827	8.2
PYHB	607	2.7	690	3.2	850	3.6	1074	3.9	1166	3.7	1334	3.9

Deprivation quintile at first prescription in period												
WIMD1	7003	32.1	6733	32.5	7411	32.0	8238	31.0	9086	30.0	9904	29.9
WIMD2	5143	23.5	4889	23.6	5290	22.9	6080	22.9	6916	22.9	7596	22.9
WIMD3	4333	19.8	4002	19.3	4597	19.9	5328	20.1	6039	20.0	6771	20.5
WIMD4	2508	11.5	2383	11.5	2815	12.2	3363	12.7	4061	13.4	4410	13.3
WIMD5	2863	13.1	2691	13.0	3021	13.1	3539	13.3	4150	13.7	4423	13.4
	21850	100.0	20698	100.0	23134	100.0	26548	100.0	30252	100.0	33104	100.0
Recorded diagnosis												
Big six non cancer pain	14165	62.3	15120	70.9	17424	72.9	20623	75.0	23619	75.5	26176	76.1
Depression/anxiety	5282	23.2	5687	26.7	6580	27.5	7843	28.5	9254	29.6	10376	30.1
More than 3 months	5122	22.5	5301	24.9	5396	22.6	6343	23.1	7395	23.6	8212	23.9
More than 6 months	1736	7.6	2370	11.1	2359	9.9	2870	10.4	3277	10.5	3681	10.7

Year	**2011**		**2012**		**2013**		**2014**		**2015**	
Number of events	37228		40898		43078		47201		61411	
Mean prescription duration days	86.11		92.34		92.86		94.74		142.24	
(SD)	149.226		169.994		169.169		181.190		332.411	
Mean age (SD)	57.50	16.531	57.35	16.371	57.47	16.268	57.56	16.189	57.76	16.040
Sex										
Male	16303	43.8	18082	44.2	18980	44.1	20980	44.4	27370	44.6
Female	20925	56.2	22816	55.8	24098	55.9	26221	55.6	34041	55.4
First opioid in prescription										
period	1736	4.7	2305	5.6	3045	7.1	3865	8.2	6316	10.3
Strong	35492	95.3	38593	94.4	40033	92.9	43336	91.8	55095	89.7
Weak										
Health Board										
ABMUHB	17927	48.2	19022	46.5	19065	44.3	19907	42.2	25647	41.8
ABUHB	4021	10.8	4629	11.3	4843	11.2	5369	11.4	7155	11.7
BCUHB	5127	13.8	6068	14.8	7122	16.5	8624	18.3	11229	18.3
CVUHB	3232	8.7	3598	8.8	3883	9.0	4417	9.4	5492	8.9
CTUHB	2284	6.1	2468	6.0	2629	6.1	2855	6.0	3826	6.2
HDUHB	3099	8.3	3478	8.5	3685	8.6	4035	8.5	5664	9.2
PYHB	1538	4.1	1635	4.0	1851	4.3	1994	4.2	2398	3.9
Deprivation quintile at first prescription in period										
WIMD1	10379	29.0	11602	29.5	11941	28.8	13129	29.0	17264	29.5
WIMD2	8310	23.3	9068	23.0	9420	22.7	10024	22.1	13012	22.2
WIMD3	7390	20.7	7928	20.1	8530	20.6	9508	21.0	12132	20.7
WIMD4	4898	13.7	5413	13.7	5911	14.3	6574	14.5	8331	14.2

WIMD5	4759	13.3	5362	13.6	5670	13.7	6066	13.4	7812	13.3
	35736	100.0	39373	100.0	41472	100.0	45301	100.0	58551	100.0
Recorded diagnosis										
Big six non cancer pain	28524	76.6	31543	77.1	33186	77.0	36292	76.9	47006	76.5
Depression/anxiety	11476	30.8	12849	31.4	13884	32.2	15282	32.4	20417	33.2
More than 3 months	8879	23.9	10380	25.4	10948	25.4	12037	25.5	19686	32.1
More than 6 months	4038	10.8	4814	11.8	5080	11.8	5593	11.8	10560	17.2

G.2 Prescribing persistence by gender

Women were recipients of 2,557,215 periods of prescribing which equated to 59.4% of the total. The proportions of women compared to men remained similar for all the prescribing persistence categories examined (Table G.3). The difference in numbers of women compared to men was statistically significant (Mann-Whitney $p<.001$, $d_{Cohen} = 3.2$, $\eta^2 = 0.72$).

G.2.1 Analysis by gender differences

Examined by gender, men were noted to have an average prescribing persistence of 8.94 ± 65.2 days and women 8.36 ± 61.9 days (Figure G.1). There was no statistical difference in prescribing persistence between genders (Mann-Whitney $p>0.05$, $d_{Cohen}= 0.1$, $\eta^2 = 0.002$). Prescription persistence increased 402.4% (from 3.39 to 17.03 days) for men between 2005 and 2015 (Table G.3). In the same period, persistence increased 333.8% (from 3.37 to 14.62 days) for women.

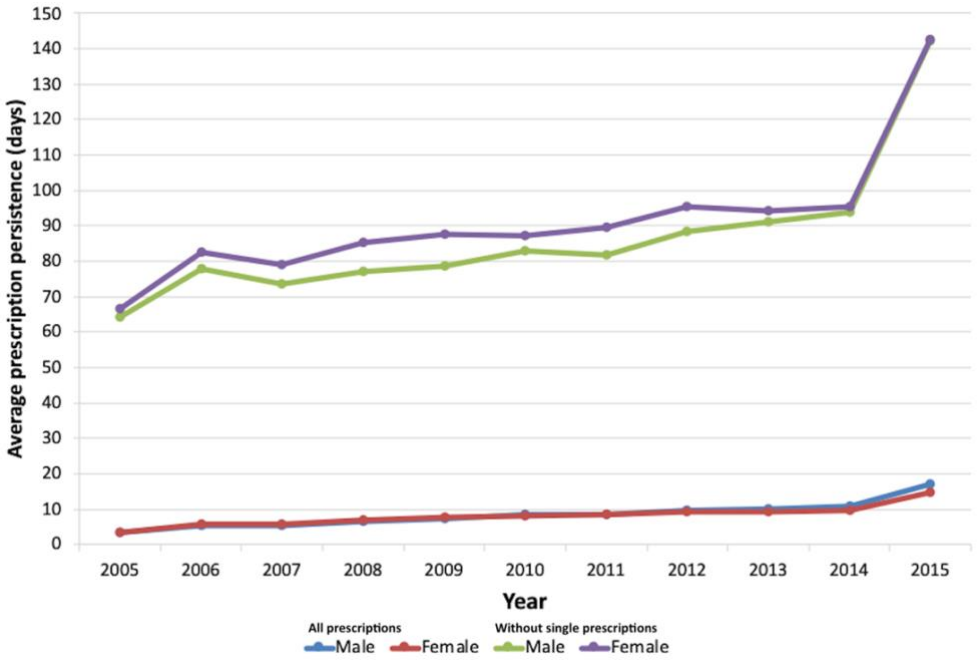


Figure G.1: Trends in prescribing persistence for all prescriptions and prescribing events with 2 or more consecutive prescriptions, stratified by gender

Although women received many more prescriptions than men during the study, there was very little difference between the average duration of prescribing persistence on an annual basis or when all data was examined (Figure G.1).

When one-off prescriptions were removed from analysis (where another prescription was not issued within 31 days from the preceding one), there was again, little difference between genders, in terms of days persistence (Table G.3). Men had a larger percentage increase in persistence but by the end of the 11 years examined, both genders were recorded as having the same prescribing persistence (Figure G.1). Unsurprisingly, a statistically significant difference in

prescribing persistence between genders was not found (Mann-Whitney p>0.05, d_{Cohen}= 0.63, η^2 =.09).

G.2.2 Extended durations of prescribing persistence by gender

Women had an average of 38% more prescribing events with a persistence of between 3 and 6 months although a greater percentage increase in the number of events was noted in men during the 11 years analysed (Table G.3). Despite the difference in the overall number of events, a statistically significant difference was not determined (Mann-Whitney p≥.05, d_{Cohen}= .94, η^2 = .2).

Table G.3: Trends in prescription persistence (in days), stratified by gender per 1000 gender-adjusted population.

	Female	Male
Mean duration (days) ±SD	8.36 ± 62.0	8.94 ± 65.2
2005	3.4 ± 21.1	3.4 ± 20.7
2015	14.6 ± 114.4	17.0 ± 124.8
Percentage increase (%)	333.8	402.4
Duration (days) without one-off doses ± SD	96.2 ± 189.1	92.8 ± 190.7
2005	66.5 ± 67.4	64.2 ± 65.0
2015	142.4 ± 330.4	142.1 ± 335.0
Percentage increase (%)	114.3	121.2
Persistence of 3 – 6 months	2813.6 ± 979.0	2033.8 ± 866.6
2005	2084	1302
2015	5117	4009
Percentage change (%)	145.5	207.9
Persistence of 3 – 6 months per 1000 population	2.32 ± 0.80	1.74 ± 0.71
2005	1.76	1.15
2015	4.18	3.37
Percentage change (%)	137.7	192.6
Persistence more than 6 months	2478.8 ± 1314.5	1737.4 ± 1120.6
2005	1115	621
2015	5914	4646
Rate change (%)	430.4	648.1
Persistence more than 6 months per 1000 population	2.04 ± 1.06	1.48 ± 0.93
2005	0.94	0.55
2015	4.83	3.91
Rate change (%)	413.5	610.9

When adjusted to gender-population, women had 33% more prescribing events with a persistence of between 3 and 6 months than men (2.32 versus 1.74 events per 1000 respectively) (Figure G.2). A larger percentage increase was noted in men (192.6%, from 1.15 to 3.37 events per 1000 population) than women (137.7%, from 1.76 to 4.18 events per 1000 population) (Table G.3). The average number of events per 1000 population, with persistence of between 3 to 6 months was not found to be statistically different (Mann-Whitney p>.05, d_{Cohen}= .91, η^2 = .17).

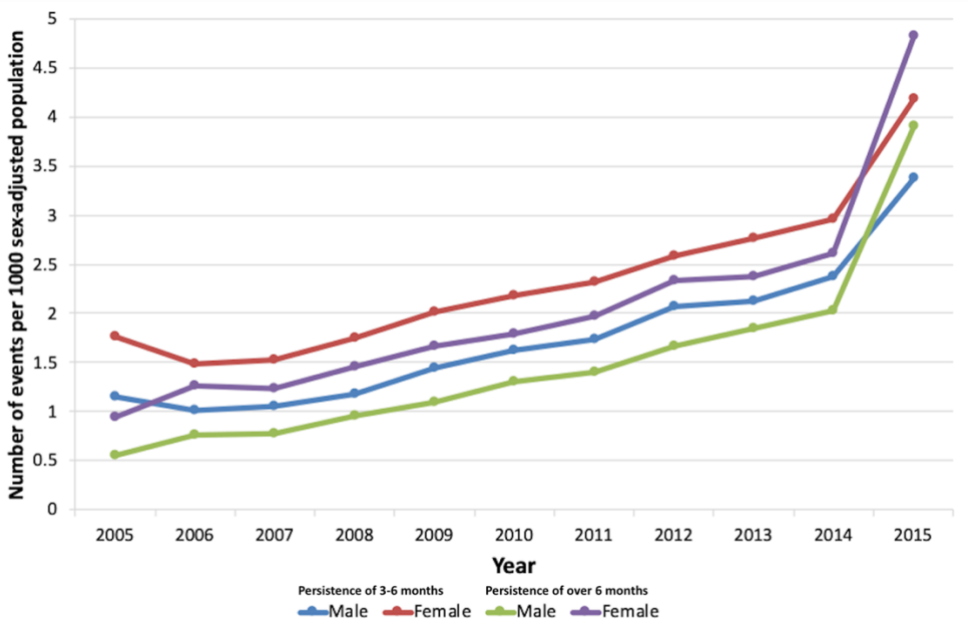


Figure G.2: Trends in the number of prescribing events with persistence of 3-6 months and over 6 months, stratified by gender

Both genders demonstrated a large increase in the number of prescribing events with a persistence of more than 6 months between 2005 and 2015 (Figure G.2). Men had the largest percentage increase (648.1%, from 621 to 4646 events) although women had an average of 43% more events than men during the study (2478.8 versus 1737.4 events respectively). Despite the difference in average number of events, there was not a statistical difference between men and women, in respect of prescribing persistence of more than 6 months (Mann-Whitney $p>0.05$, $d_{Cohen}= 0.80$, $\eta^2 = 0.14$). Adjusting for population lead to little change in the differences noted between men and women (Table G.3) and no statistical difference was noted in number of events per 1000 (Mann-Whitney $p>0.5$, $d_{Cohen}= 0.73$, $\eta^2 = 0.12$) between 2005 and 2015.

G.3 Analysis by age-group

Mean average prescribing persistence ranged from 1.9 days (SD = 0.65) for the 18-24 years age-group to 10.1 days (SD = 1.8) in the 85 years and over age-group (Table G.4). Average duration of prescription persistence, when all prescriptions were included, was significantly different between the 6 age-groups used in the study (Kruskal-Wallis $p<0.01$, $d_{Cohen} = 1.97$, $\eta^2 =0.492$). Dunn's pairwise analysis confirmed statistically significant differences between the youngest (18-24 years) and all age groups aged 45 and over (Table G.5). Statistically significant differences did not exist between any of the other age groups, in relation to the average duration of prescribing persistence.

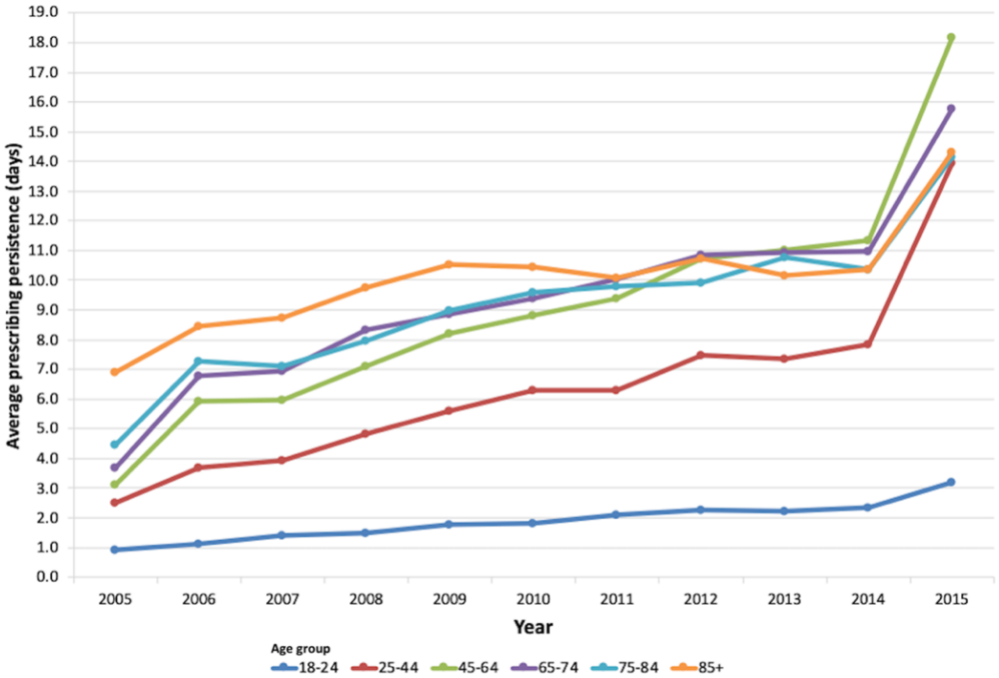


Figure G.3: Trends in average prescription persistence 2005 - 2015, stratified by age-group

Between 2005 and 2015, the largest increase in prescription persistence days was noted in the 45 – 64 years group (481.5%, from 3.1 to 18.2 days) (Figure G.3). That age-group had the longest average prescribing persistence (18.2 days) in 2015, despite the oldest age-group (≥ 85 years) having the highest average duration during the study (Table G.4).

Removing all single prescription events i.e. when a prescription was not followed by a subsequent prescription within 31 days, resulted in average durations lengthening (Table G.4) with a range from 43.7 days (18 -24 years) to 103.9 days (≥ 85 years) – again, the older age groups had prescribing persistence of around double that of the youngest people receiving prescribed opioids (Figure G.4).

Table G.4: Trends in prescribing persistence (in days), stratified by age group.

Mean annualised data 2005 – 2015 (SD)	**Age group (years)**					
	18 – 24	25 – 44	45 – 64	65 – 74	75 – 84	≥85
Duration in days	1.9 (0.65)	6.4 (3.1)	9.1 (3.9)	9.3 (3.1)	9.2 (2.5)	10.1 (1.8)
2005	0.9	2.5	3.1	3.7	4.5	6.9
2015	3.2	14.0	18.2	15.8	14.2	14.3
Percentage increase (%)	245.2	456.2	481.5	325.9	217.0	107.5
Duration without one-off doses	43.7 (6.1)	78.8 (21.6)	89.3 (21.8)	95.1 (17.4)	98.9 (17.2)	103.9 (15.2)
2005	37.3	61.0	65.2	68.1	68.1	71.7
2015	60.8	140.2	149.4	138.9	139.3	137.1
Percentage increase (%)	63.0	130.0	129.0	103.9	104.5	91.2
Number of annual events *per 1000 population*	18988.1 (1353.9)	84505.7 (11169.9)	142492.1 (26426.9)	67126.4 (14737.1)	44858.6 (8747.4)	17694.8 (2615.0)
Weak opioid	*65.8 (3.5)*	*111.8 (16.4)*	*178.2 (31.4)*	*220.8 (38.5)*	*236.8 (41.6)*	*243.5 (36.6)*
per 1000 population	185.5 (122.0)	2593.9 (1562.1)	6506.0 (4351.8)	2955.0 (1861.0)	2342.8 (1170.4)	1390.6 (591.7)
Strong opioid	*0.6 (0.4)*	*3.5 (2.2)*	*8.1 (5.3)*	*9.4 (5.0)*	*12.3 (5.7)*	*18.7 (6.7)*
per 1000 population						
Number of events						
Male	7274.4 (1353.9)	37882.7 (4701.1)	65666.2 (13277.6)	28862.5 (7319.4)	15326.9 (3629.8)	4152.7 (869.4)
Per 1000 population	*51.5 (2.3)*	*102.2 (14.1)*	*167.4 (31.3)*	*192.9 (35.7)*	*164.7 (34.0)*	*115.9 (19.5)*
Female	11899.2 (1243.0)	49216.9 (8068.4)	83331.9 (17270.9)	41218.9 (9137.7)	31874.5 (6168.6)	14932.6 (2259.2)
Per 1000 population	*80.9 (7.0)*	*127.8 (23.0)*	*204.4 (41.0)*	*266.0 (48.1)*	*330.1 (58.2)*	*402.8 (60.4)*
Persistence of 3 – 6 months	51.7 (19.1)	754.2 (290.9)	2057.5 (906.0)	1011.7 (395.4)	668.8 (183.1)	303.5 (77.3)
Per 1000 population	*0.2 (0.1)*	*1.0 (0.4)*	*2.6 (1.1)*	*3.3 (1.0)*	*3.5 (0.9)*	*4.2 (1.0)*
2005	0.12	0.71	1.39	2.71	3.45	5.87
2015	0.30	1.97	4.99	5.55	5.59	5.98
Rate increase (%)	144.2	178.0	258.2	104.9	62.0	1.7
Persistence more than 6 months	32.9 (18.1)	673.9 (439.3)	1747.6 (1132.0)	888.2 (490.5)	592.1 (267.9)	281.5 (90.1)
Per 1000 population	*0.1 (0.1)*	*0.9 (0.6)*	*2.2 (1.4)*	*2.8 (1.3)*	*3.1 (1.3)*	*3.8 (1.0)*
2005	0.03	0.34	0.80	1.32	1.66	3.08
2015	0.27	2.51	5.73	6.21	6.44	6.60
Rate increase (%)	703.8	641.0	619.8	370.8	287.6	114.0
Depression and/or anxiety	6594.7 (343.0)	35005.5 (6516.5)	46654.7 (13720.1)	14104.2 (4380.4)	7702.8 (1722.6)	2596.7 (749.3)
Per 1000 population	*22.9 (1.7)*	*46.4 (9.4)*	*58.2 (16.2)*	*46.0 (10.5)*	*40.6 (7.8)*	*35.2 (7.8)*

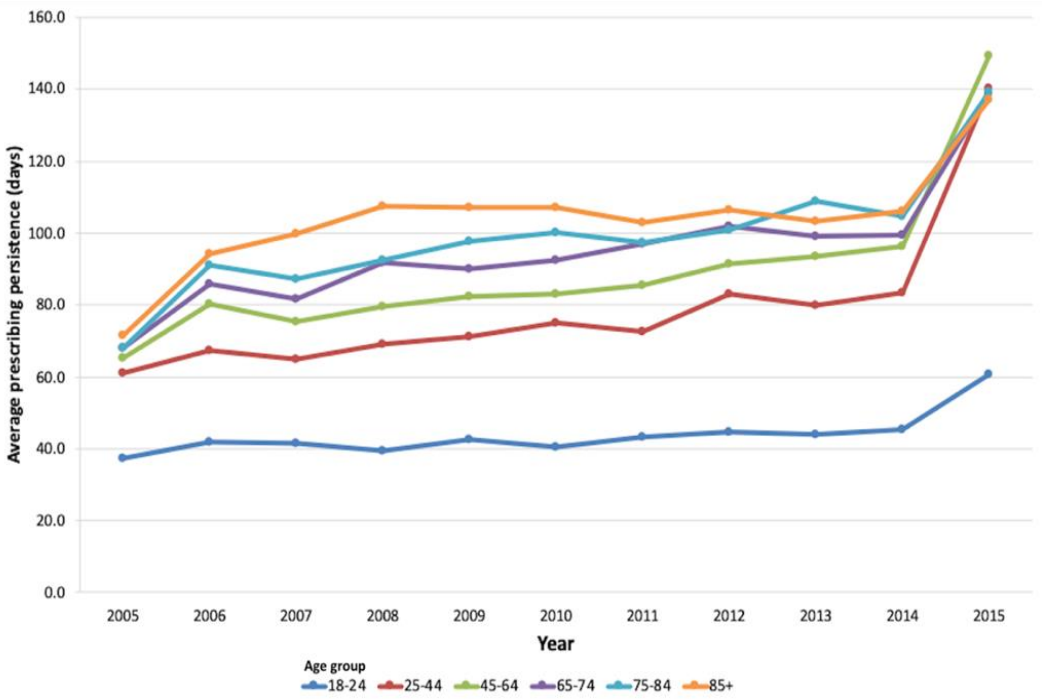


Figure G.4: Trends in prescription persistence 2005 - 2015 using data from people who received more than 1 prescription within a 31-day period, stratified by age group

The largest increase in prescription persistence (days) between 2005 and 2015, was noted in the 45 – 64 years age-group, from 3.1 to 18.2 days (481.5%). People aged 85 years and over had the smallest increase in prescribing persistence during the study period, even so, the duration doubled over the time examined. Statistically significant differences in the average duration of prescribing persistence were demonstrated between the age-groups (Kruskal-Wallis $p<0.01$, $d_{Cohen} = 2.4$, $\eta^2 = 0.6$). Post-hoc analyses confirmed significant differences in average prescribing persistence between the youngest age group (18 – 24 years) and groups ≥ 65 years and those aged 25 – 44 and the oldest age-group (≥ 85 years). Statistical differences in prescribing persistence were not confirmed between any other age-groups (Table G.6).

All six age-groups were noted to have large increases in prescribing persistence (days) in 2015, this was due to the manner of data extraction and analysis resulting in people with the longest durations of prescribing, being recorded in 2015 rather than the year their prescriptions were initiated

Persistent periods of prescribing between 3 and 6 months, were most frequent in the 45 – 64 years age-group (Figure G.5). When adjusted per 1000 age-group population however, the rate of prescribing persistence increased with increasing age-group. The largest percentage increase in prescribing persistence was in the 45 – 64 years age-group (258.2%, from 1.39 to 4.99 events per 1000 population).

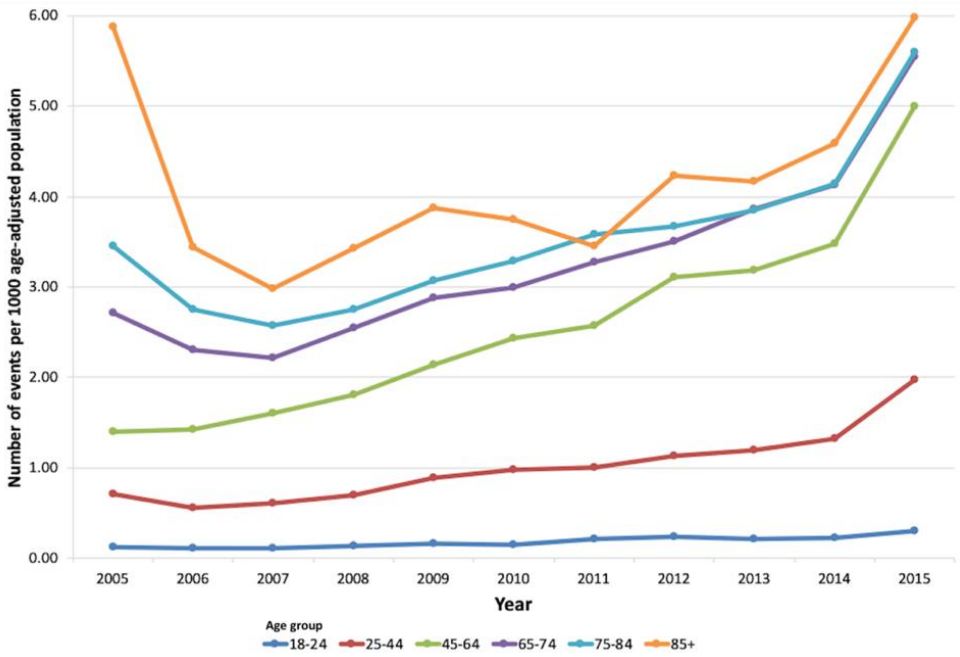


Figure G.5: Trends in the number of events with a prescribing persistence of between 3 and 6 months, between 2005 and 2015 and stratified by age-group

More than 40 times more events with a prescribing persistence of between 3 and 6 months were recorded in the 45 – 64 years age-group compared to 18 – 24 years. When adjusted to population, there was a 35 times difference between the average incidence in the youngest (0.2 per 1000 population) and oldest age-group (4.2 per 1000 population) (Table G.8).

Average numbers of events where people received prescriptions for 3 and 6 months were determined to be significantly different ($p<.001$, $d_{Cohen}= 4.6$, $\eta^2 =0.8$) between the six age-groups. Those differences were confirmed between the youngest age group (18 – 24 years) and all age-groups between 25 and 84 years old. Statistically significant differences were not confirmed between the youngest and oldest age groups. Statistically significant differences were confirmed between the 65 – 74 and ≥85 years group and the 45 – 64 years and 75 – 84 years groups (Table G.7).

Table G.5: Dunn's pairwise comparisons and Bonferroni correction output for average prescribing duration of all prescribing events 2005 – 2015, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	.291				
45-64	.001	>.999			
65-74	<.001*	.567	>.999		
75-84	<.001*	.852	>.999	>.999	
85+	<.001*	.136	>.999	>.999	>.999

*p<0.05 = statistically significant

Table G.6: Dunn's pairwise comparisons and Bonferroni correction output for average prescribing duration for events with at least two prescriptions issued per individual, 2005 – 2015, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84

25-44	.347				
45-64	.014*	>.999			
65-74	<.001*	.852	>.999		
75-84	<.001*	.170	>.999	>.999	
85+	<.001*	.013*	.332	>.999	>.999

*p<0.05 = statistically significant

Table G.7: Dunn's pairwise comparisons and Bonferroni correction output for numbers of events with prescribing persistence between 3 and 6 months per 1000 population, 2005 – 2015, stratified by age-group

Age group (years)	**18-24**	**25-44**	**45-64**	**65-74**	**75-84**
25-44	>.999				
45-64	.008*	.567			
65-74	<.001*	.034*	>.999		
75-84	<.001*	.005*	>.999	>.999	
85+	<.001*	<.001*	.229	>.999	>.999

*p<0.05 = statistically significant

Table G.8: Combined prescribing persistence descriptive data 2005 - 2015, stratified by age group

Age group	18-24		25-44		45-64		65-74		75-84		85+	
Number of events	210909		958096		1638979		770895		519215		209939	
Mean prescription duration days (SD)	1.92 (.65)		6.66		9.64		9.70		9.31		10.19	
Sex												
Male	80018	37.9	416710	43.5	722328	44.1	317487	41.2	168596	32.5	45680	21.8
Female	130891	62.1	541386	56.5	916651	55.9	453408	58.8	350619	67.5	164259	78.2
First opioid in prescription period												
Strong	2040	1.0	28533	3.0	71566	4.4	32505	4.2	25771	5.0	15296	7.3
Weak	208869	99.0	929563	97.0	1567413	95.6	738390	95.8	493444	95.0	194643	92.7
Health Board												
ABMUHB	50695		251978		430035		202108		141490		57664	
ABUHB	33031		164080		299033		134697		85053		30483	
BCUHB	41726		187903		318529		162394		104034		42245	
CVUHB	39148		155655		217170		90703		67851		29250	
CTUHB	20045		95691		178234		83560		53756		20447	
HDUHB	21945		82587		154038		76793		53260		24459	
PTHB	4319		20202		41940		20640		13771		5391	
Deprivation quintile at first prescription in period												
WIMD1	58829	29.8	279078	30.3	446213	28.2	177971	24.0	109684	22.0	39309	19.9
WIMD2	43302	21.9	210530	22.8	358300	22.7	163061	21.9	105533	21.1	40822	20.7
WIMD3	37199	18.8	177729	19.3	318475	20.2	157780	21.2	108064	21.6	44116	22.4
WIMD4	29252	14.8	131741	14.3	236297	15.0	124223	16.7	84598	16.9	35089	17.8
WIMD5	28935	14.6	122363	13.3	220507	14.0	120037	16.2	91464	18.3	37849	19.2
Recorded diagnosis												
Big six non cancer pain	101497	48.1	661298	69.0	1255494	76.6	585956	76.0	381269	73.4	136983	65.2
Depression/anxiety	72542	34.4	385060	40.2	513202	31.3	155146	20.1	84731	16.3	28564	13.6
Buprenorphine	367		6205		19670		11616		13148		10570	
Codeine	163001		653905		1025221		482228		328675		133699	
Dextropropoxyphene	354		4806		17321		13569		10310		3606	
Dihydrocodeine	28667		137669		260459		130535		84148		28847	
Fentanyl	162		2652		9464		5966		7216		6503	
Morphine	1130		16751		41456		18074		13286		6561	
Oxycodone	501		5399		12239		5208		3198		1261	
Tapentadol	10		344		755		150		133		37	
Tramadol	16562		128652		248738		102404		58534		18657	
Other	155		1713		3656		1145		567		198	

G.3.1.1 Extended durations of prescribing persistence by age-group

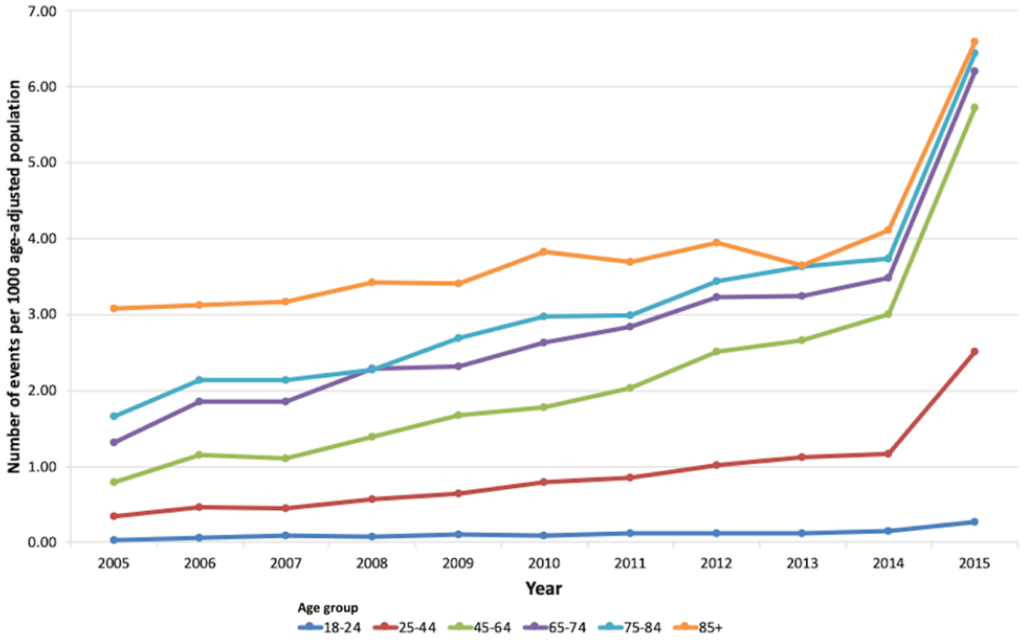


Figure G.6: Trends in the number of events with prescribing persistence of over 6 months, between 2005 and 2015 and stratified by age-group per 1000 age-adjusted population

Mean prescribing persistence of more than 6 months was highest by number of events in the 45 – 64 years age-group (1747.6 events). Statistically significant differences were demonstrated between all the age groups ($p<.001$ $D_{Cohen}= 3.6$, $\eta^2 =0.8$). Statistical significantly fewer events were confirmed in the youngest age group compared all those of 25 to 84 years. Significantly more events with persistence of more than six months were confirmed in those age 85 years and over compared to people aged between 45 and 74 years (Table G.9). Differences between all other age-groups receiving prescriptions for more than 6 months were not confirmed (Table G.9).

When adjusted to age-group population, the oldest age-group (≥ 85 years) had the highest rate of prescribing persistence over 6 months (3.8 events per 1000 population) (Table G.4). The largest increase in the rate of persistence of over 6 months, was in the youngest age group (703.8%, from 0.03 to 0.27 events per 1000 population) between 2005 and 2015. There were an average 38 times more prescribing events of over 6 months in the oldest age group in the same period although the percentage increase was much less, (114% increase, from 3.08 to 6.6 events per 1000 population).

Statistical analysis confirmed significant differences between the rate of prescribing persistence for the different age-groups (Kruskal-Wallis $p<.001$, $\eta^2 =0.7$, $d_{Cohen}= 3.4$). People aged 18 – 24 years age-group were confirmed to have significantly lower prescribing rates compared to ages above 45 years but not with those aged 25 – 44 years old (Table G.10). A significantly lower prescribing rate was also confirmed in the 25 – 44 yeas age-group compared to the two oldest groups (≥75 years old) (Table G.10).

Table G.9: Dunn's pairwise comparisons and Bonferroni correction output for numbers of events with prescribing persistence greater than 6 months, 2005 – 2015, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	>.999				
45-64	.013*	>.999			
65-74	<.001*	.077	>.999		
75-84	<.001*	.024*	>.999	>.999	
85+	<.001*	<.001*	.091	>.999	>.999

*p<0.05 = statistically significant

Table G.10: Dunn's pairwise comparisons and Bonferroni correction output for numbers of events with prescribing persistence greater than 6 months per 1000 population, 2005 – 2015, stratified by age-group

Age group (years)	18-24	25-44	45-64	65-74	75-84
25-44	0.002*				
45-64	0.003*	0.212			
65-74	<.001*	>.999	>.999		
75-84	0.003*	>.999	0.150	>.999	
85+	>.999	0.352	<.001*	>.999	0.481

*p<0.05 = statistically significant

G.4 Prescribing persistence by deprivation

Mean duration (days) of prescription persistence was 54% longer (10.3 days versus 6.7 days) in the most deprived areas (WIMD) of Wales, compared to the least deprived (WIMD5), between 2005 and 2015 respectively (Table G.15). Differences in mean persistence were statistically significant (Kruskal-Wallis $p<0.05$, $\eta^2 = 0.12$, $d_{Cohen} = 0.75$) when all quintiles were compared (Figure G.7). However, pairwise comparisons did not confirm any significant difference between any of the quintiles (Table G.11).

During the 11 years examined, persistence increased by more than 4 times in all quintiles (Figure G.7). The second least deprived areas (WIMD4) had the greatest increase (391.3%, from 2.5 to 12.3 days). Most deprived areas (WIMD1), where persistence was longest throughout the study, had a similar level of increase (389.3, from 4.0 to 19.3 days) (Table G.15).

Prescription persistence, when single events were removed from the analysis, showed less variance in duration between the quintiles, with a 22% (101.3 days versus 82.8 days) between WIMD1 and WIMD5 areas respectively (Table G.15). Prescription persistence was similar for all quintiles, when examining only multiple prescription issues (Figure G.8). This was the case until 2015 when there was a large increase in duration, due to the inclusion in that year's data of prescribed events which originated in the early years of the study.

Whilst a statistically significant difference between mean prescribing persistence was determined (Kruskall-Wallis $p<0.01$, $\eta^2 = 0.2$, $d_{Cohen} = 1.0$) pairwise comparison (Figure G.8) failed to confirm any significant differences between quintiles (Table G.12).

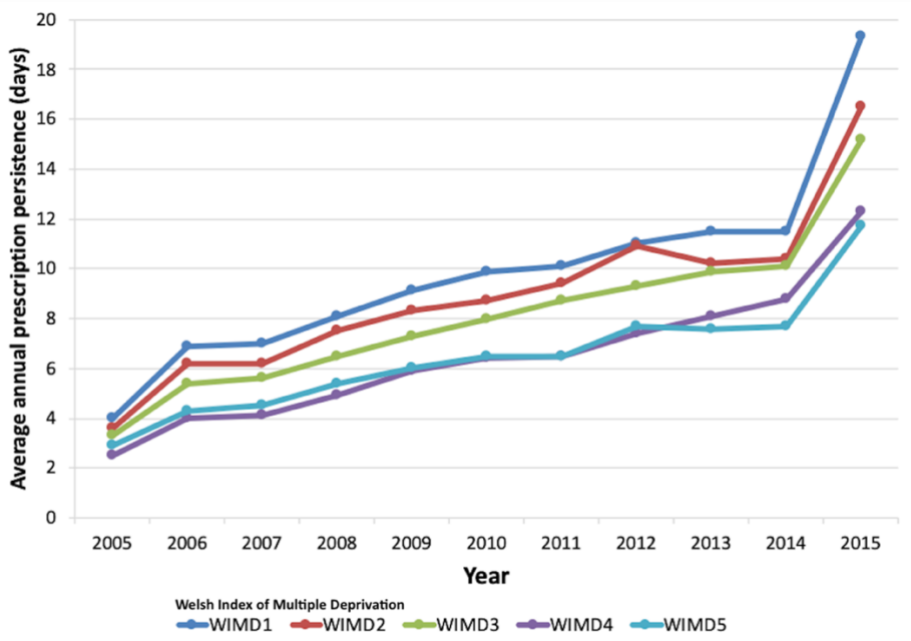


Figure G.7: Trends in average annual prescribing persistence (days) stratified by Welsh Index of Multiple Deprivation quintiles. WIMD1=most deprived, WIMD5 = least deprived

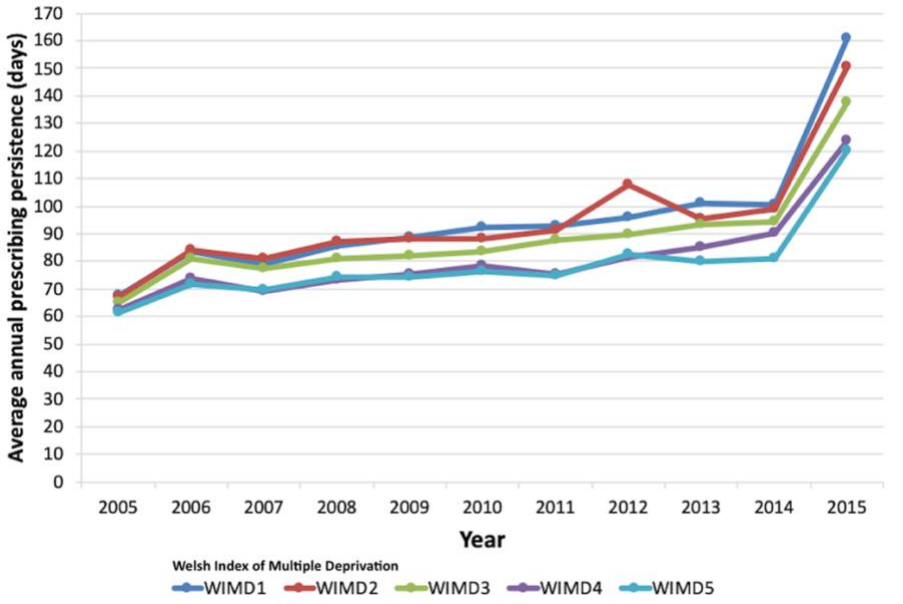


Figure G.8: Trends in average annual prescribing persistence (days) for events of two or more prescriptions issued within 32 days, stratified by Welsh Index of Multiple Deprivation quintiles.
WIMD1=most deprived, WIMD5 = least deprived

G.4.1.1 Extended durations of prescribing persistence by deprivation

Prescribing events with a persistence of between 3 and 6 months, averaged more than double the number in the most deprived areas of Wales, compared to the least deprived (1467.3 in WIMD1 compared to 630.8 in WIMD5) (Table G.15). Mean event numbers showed a large variance between quintiles WIMD1-3, the most deprived areas, compared to WIMD4-5 areas, although there were an average 37% more prescribing events of between 3-6 months in WIMD1 areas compared to WIMD2 (1069.7) in the 11 years analysed.

A statistically significant difference was demonstrated between the number of events with a persistence of between 3 and 6 months in each quintile (Kruskal-Wallis $p<.001$, $\eta^2 =0.4$, $d_{Cohen}= 1.8$). Pairwise comparison confirmed significant differences between the number of events occurring in WIMD4 areas compared to WIMD1 and WIMD2 areas respectively and WIMD5 and WIMD1 areas (Table G.13).

Table G.11: Dunn's pairwise comparison and Bonferroni post-hoc analysis of mean prescribing persistence (days), in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	.117	.570	>.999	
5	.123	.597	>.999	>.999

*p-value <0.05 = statistically significant WIMD1=most deprived, WIMD5-least deprived

Table G.12: Dunn's pairwise comparison and Bonferroni post-hoc analysis of mean prescribing persistence (days) when events not repeated within 31 days were removed from analysis, in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	>.999	>.999		
4	.154	.192	>.999	
5	.046*	.059	.643	>.999

*p-value <0.05 = statistically significant. WIMD1=most deprived, WIMD5-least deprived

Table G.13: Dunn's pairwise comparison and Bonferroni post-hoc analysis of average number of events with a prescribing persistence between 3 - 6 months, in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	.222	>.999		
4	<.001*	.040*	.455	
5	<.001*	.083	.812	>.999

*p-value <0.05 = statistically significant WIMD1=most deprived, WIMD5-least deprived

Table G.14: Dunn's pairwise comparison and Bonferroni post-hoc analysis for number of events per 1000 population with prescribing persistence between 3 - 6 months, in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	.332	>.999		
4	<.001*	.093	.431	
5	<.001*	.027*	.157	>.999

*p-value <0.05 = statistically significant WIMD1=most deprived, WIMD5-least deprived

Table G.15: Trends in prescribing persistence between 2005 and 2015, stratified by Welsh Index of Multiple Deprivation (WIMD) quintile where WIMD1 = most deprived and WIMD5 = least deprived

	Welsh Index of Multiple Deprivation quintile				
	WIMD1	**WIMD2**	**WIMD3**	**WIMD4**	**WIMD5**
Mean duration (days) ±SD	10.3 ± 72.0	9.3 ± 67.6	8.5 ± 61.4	6.8 ± 52.8	6.7 ± 51.5
2005	4.0 ± 22.8	3.6 ± 21.6	3.3 ± 20.7	2.5 ± 18.2	2.9 ± 19.2
2015	19.3 ± 140.1	16.5 ± 125.2	15.2 ± 112.5	12.3 ± 96.4	11.7 ± 96.4
Percentage increase (%)	389.3	358.4	358.9	391.3	306.6
Duration without one-off doses (SD)	101.3 ± 204.8	99.5 ± 200.5	93.7 ± 183.2	86.1 ± 168.7	82.8 ± 162.7
2005	67.4 ± 67.7	67.0 ± 66.5	65.2 ± 66.2	62.5 ± 65.8	61.5 ± 64.9
2015	160.6 ± 374.6	150.6 ± 351.0	137.7 ± 313.0	123.5 ± 281.6	120.0 ± 286.6
Percentage increase (%)	138.3	124.7	111.1	97.7	95.0
Persistence of 3 – 6 months ± SD	1467.3 ± 502.7	1069.7 ± 365.1	934.6 ± 366.2	600.3 ± 287.6	630.8± 274.4
2005	1091	793	630	353	370
2015	2685	1866	1807	1232	1116
Percentage change (%)	146.1	135.3	186.8	249.0	201.6
Persistence of 3 – 6 months per 1000 population ± SD	3.0 ± 1.0	2.2 ± 0.7	2.0 ± 0.8	1.3 ± 0.6	1.2 ± 0.5
2005	2.03	1.39	1.23	0.62	0.64
2015	5.48	3.8	3.83	2.66	2.25
Percentage change	138.1	126.4	173.4	231.4	190.4
Persistence more than 6 months ± SD	1308.6 ± 738.0	984.0 ± 537.2	824.6 ± 479.6	490.8 ± 321.4	508.5 ± 308.2
2005	564	406	332	175	204
2015	3262	2376	2051	1311	1114
Rate change (%)	478.4	485.2	517.8	649.1	446.1
Persistence more than 6 months ± SD	2.5 ± 1.5	2.0 ± 1.1	1.8 ± 1.0	1.1 ± 0.7	0.9 ± 0.5
2005	1.19	0.86	0.74	0.40	0.43
2015	6.65	4.84	4.35	2.84	2.24
Rate change	459.5	463.0	488.9	611.4	425.7

When adjusted to population, the average number of prescribing events with a persistence between 3 and 6 months was 2.5 times greater in the most deprived areas of Wales (WIMD1 = 3.0 events per 1000 population) than the least deprived (WIMD5 = 1.2 events per 1000 population) (Figure G.9). Increases in the number of events per 1000 population were smallest in the two most deprived areas (Table G.15) although the overall numbers of events were higher in those areas compared to the lesser deprived quintiles. Significant differences were demonstrated between the number of events per 1000 population when all quintiles were compared (Kruskal-Wallis $p<.001$, $\eta^2 = 0.5$, $d_{Cohen} = 2.0$). WIMD1 quintile areas were confirmed to have significantly more events than the two least deprived quintile areas (WIMD4 and WIMD5 respectively). Confirmation of significantly more events in WIMD2 areas compared to WIMD5 areas was demonstrated from pairwise comparison as well. Significance was not confirmed when all other areas were compared pairwise

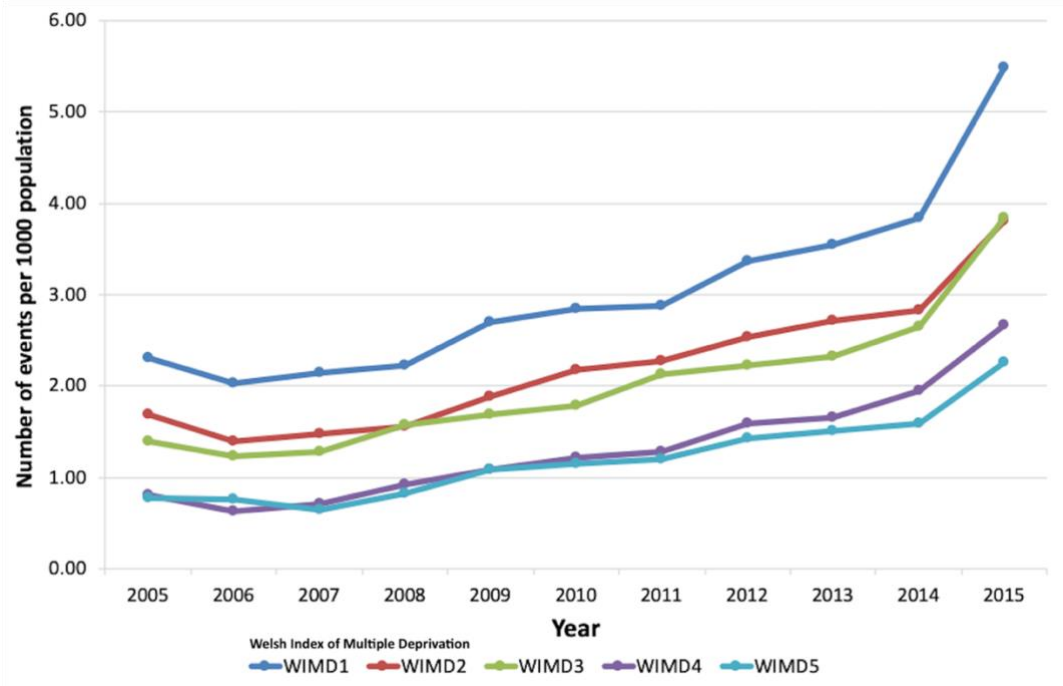


Figure G.9: Trends in prescription persistence of 3-6months in events per 1000 deprivation adjusted population. WIMD1 = most deprived, WIMD5 = least deprived

Data for prescribing persistence of over 6 months showed similar trends between 2005 and 2015, as shown for durations of 3 - 6 months (Table G.15). There were 2.5 times more events of over 6 months in the most deprived areas (WIMD1 = 1308.6 events per 1000 population) compared to the least deprived (WIMD5 = 508.5 events per 1000 population). In this instance, however, on average, there were fewer events with a persistence of over 6 months in WIMD4 areas (WIMD4 = 490.8 events per 1000 population) (Figure-G.10). WIMD4 areas are classified as the second least deprived areas in Wales.

Initial analysis demonstrated a significant difference between quintiles in the number of events with more than 6 months persistence (Kruskal-Wallis $p<.001$,

η^2 =0.4, d_{Cohen}= 1.5). Confirmation of those differences was only confirmed between the most deprived areas (WIMD1) and two least deprived quintiles (WIMD4 and WIMD5) when all groups were subjected to pairwise comparison).

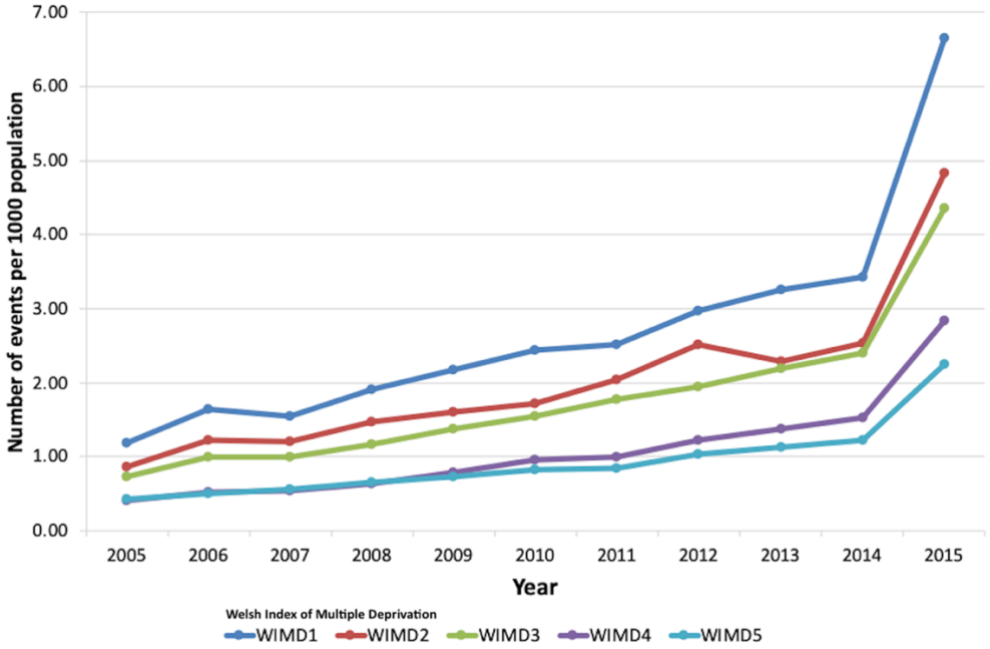


Figure-G.10: Trends in prescription persistence of over 6months in events per 1000 deprivation adjusted population. WIMD1 = most deprived, WIMD5 = least deprived

When adjusted to population, data regained a pattern of increasing number of events with increasing level of deprivation (Figure-G.10). Nearly three times as many events with a persistence of more than 6 months occurred on average in the most deprived areas (WIMD1 = 2.7 events per 1000 population), compared with the least (WIMD5 = 0.93 events per 1000 population). Large percentage increases were noted in the number of events per 1000 population with a persistence of over 6 months in all quintiles (Table G.15), the largest in WIMD4 areas (611.4%, from 0.4 to 2.84 events per 1000 population). Again, a sudden increase in the number of events per 1000 population, were noted in all areas in 2015. This was due to the inclusion in that year's data of long-term prescribing the last date of which occurred in 2015. That there was a 3 times difference between the highest number of events and lowest suggests that long-term prescribing is more likely to occur in the most deprived areas of Wales (Figure-G.10).

Table G.16: Dunn's pairwise comparison and Bonferroni post-hoc analysis of average number of events with a prescribing persistence greater than 6 months, in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	.653	>.999		
4	.002*	.068	.580	
5	.002*	.071	.625	>.999

*p-value <0.05 = statistically significant. WIMD1=most deprived, WIMD5-least deprived

Table G.17: Dunn's pairwise comparison and Bonferroni post-hoc analysis for number of events per 1000 population with prescribing persistence greater than 6 months, in the 5 different areas of deprivation as defined by the Welsh Index of Multiple Deprivation (WIMD)

	Welsh Index of Multiple Deprivation			
	1	2	3	4
2	>.999			
3	.872	>.999		
4	.003*	.078	.536	
5	.001*	.021*	.192	>.999

*p-value <0.05 = statistically significant. WIMD1=most deprived, WIMD5-least deprived

The difference in number of events per 1000 population were determined to be significant (Kruskal-Wallis p<.001, η^2 =0.4, d_{Cohen}= 1.6). Significantly more events occurred in WIMD1 and WIMD2 areas when compared pairwise to the WIMD5 quintile. There were statistically significantly more events of >6 months persistence in WIMD1 than WIMD4 areas also (Table G.16).

G.5 Prescribing persistence by opioid type

Weak opioids, as defined for this study were prescribed at the end of 4,132,324 (95.9%, 158.4 events per 1000 population) of all the prescribing periods recorded between 2005 and 2015 (Table G.18). However, as persistence of consecutive prescriptions increased, so did the percentage of strong opioids. When prescriptions were issued for ≥181 days, 4,279 (9.2%, 0.2 events per 1000 population) of those periods ended with a strong opioid prescription.

Examination by individual drug showed codeine to be by far, the most frequently prescribed drug for all prescription persistence durations (Table G.18). For all durations of prescribing persistence, codeine was the final prescription for 64.7% (2,786,730 of 4,308,035 events) of all events (Figure G.11). Codeine was also the drug of choice for nearly two thirds of short-term prescribing, where persistence was less than 32 days. As prescribing persistence increased, the percentage where codeine was given, reduced. When prescribing persisted for more than 6 months (≥181 days), codeine reduced to 52.8% of prescriptions (Table G.18).

Table G.18: Prescribing persistence stratified by drug, totalled for 2005 - 2015

	Number of prescribing events with duration prescription persistence (days) (% of total for that duration)				
Drug category	All	≤31	≥32 ≤90	≥91	≥181
Buprenorphine	61576 (1.4)	56511 (1.4)	2309 (2.1)	2756 (2.8)	1355 (2.9)
Codeine	2786730 (64.7)	2670480 (65.2)	63006 (56.1)	53244(53.4)	24480 (52.8)
Dextropropoxyphene	49966 (1.2)	48676 (1.2)	742 (0.7)	548 (0.5)	231 (0.5)
Dihydrocodeine	670326 (15.6)	635380 (15.5)	18498 (16.5)	16448 (16.5)	7638 (16.5)
Fentanyl	31963 (0.7)	29462 (0.7)	1097 (1.0)	1404 (1.4)	702 (1.5)
Morphine	97258 (2.3)	88106 (2.2)	4281 (3.8)	4871 (4.9)	2483 (5.4)
Oxycodone	27806 (0.6)	25467 (0.6)	1038 (0.9)	1301 (1.3)	655 (1.4)
Tapentadol	1429 (0.03)	1214 (0.03)	92 (0.08)	123 (0.12)	56 (0.12)
Tramadol	573547 (13.3)	533687 (13.0)	21080 (18.8)	18780 (18.8)	8673 (18.7)
Other	7434 (0.2)	6969 (0.2)	241 (0.2)	224 (0.2)	105 (0.2)

Conversely, tramadol classified as a weak opioid for this study, increased its representation, in percentage terms as prescribing persistence increased (Table G.18). This was also the case with dihydrocodeine, the third most prescribed weak opioid, albeit the percentage change was small.

The drugs categorised as strong opioids; buprenorphine, fentanyl, morphine, oxycodone and tapentadol doubled in their percentage representation as prescribing persistence increased (Table G.18). Morphine accounted for 2.2% of periods with a persistence of less than 32 days, but 5.4% of periods with a duration of more than 6 months (Figure G.11).

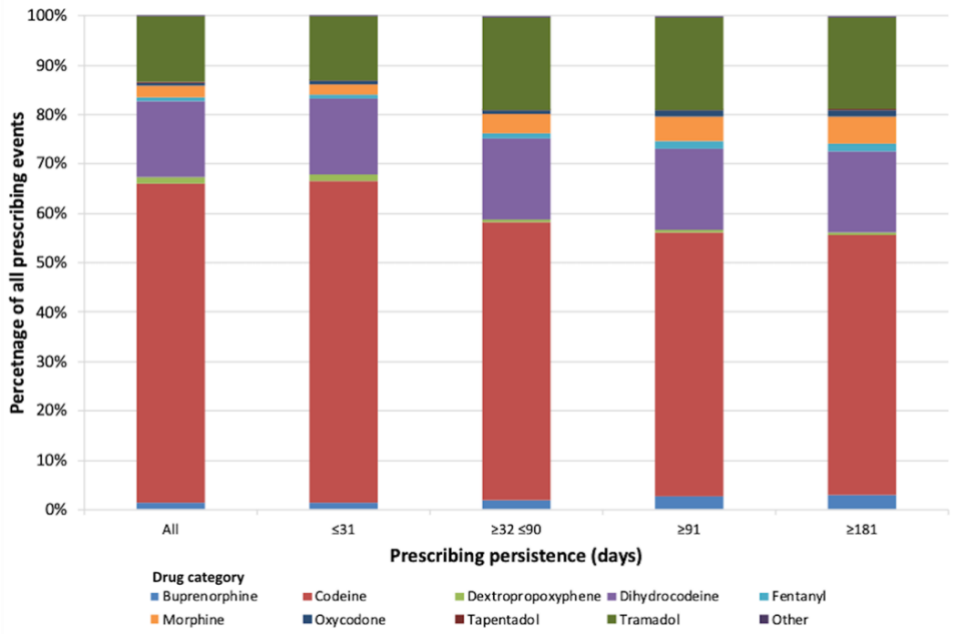


Figure G.11: Percentage contribution to prescribing persistence by drug, stratified by number of continuous days

Drugs classified as 'strong' opioids for this study, were demonstrated to have the longest average persistence in prescribing over the 11 years examined (Table G.21). Morphine, the most frequently prescribed strong opioid, had the longest average prescribing persistence when examined by all prescriptions (97,258 events in total, 19.6 ± 117.1 days) and when single prescriptions were excluded from analysis (13,752 events, 138.4 ± 283.9 days). Codeine, which was the most prescribed opioid in Wales between 2005 and 2015 had the second shortest average persistence (2,786,729 events, 7.1 ± 55.0 days and 223,077 events, 88.9 ± 174.8 days for all data and 2 or more prescriptions in a period, respectively). The 'other' opioid group (Figure G.11) had the shortest prescribing persistence for all categories that were examined (Table G.21).

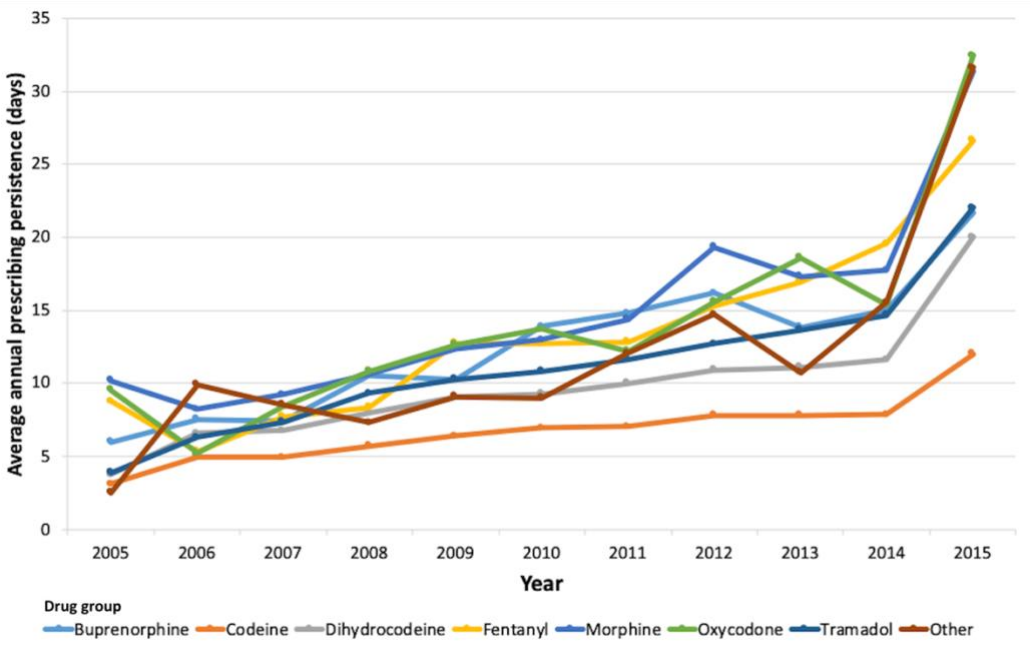


Figure G.12: Trends in average annual prescribing persistence between 2005 - 2015, stratified by drug group

The 'other' group of opioids had the largest percentage increase in average prescribing persistence (1177.2%, from 2.5 to 31.6 days), which on examination was due to the inclusion of tapentadol in that group, causing a steep incline in persistence towards the end of the study. By 2015, the prescribing persistence of 'other' opioids was similar to that of morphine and oxycodone (Figure G.12).

No statistically significant difference was determined between the duration of prescribing persistence of each drug group (Kruskal-Wallis $p<0.005$, $D_{Cohen}=0.9$, $\eta^2=0.2$). Pairwise comparison confirmed codeine had a significantly shorter duration of persistence compared to morphine, oxycodone, and fentanyl. No difference was confirmed between the persistence any of the other drug groups when directly compared (Table G.19).

Table G.19: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between average prescribing persistence (days) by drug for all prescriptions

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	0.052						
Dihydrocodeine	>.999	>.999					
Fentanyl	>.999	.032*	>.999				
Morphine	>.999	.003*	.895	>.999			
Oxycodone	>.999	.013*	>.999	>.999	>.999		
Tramadol	>.999	.410	>.999	>.999	>.999	>.999	
Other	>.999	.444	>.999	>.999	>.999	>.999	>.999

*p<0.05 is statistically significant

Table G.20: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between average prescribing persistence (days) by drug where events not repeated within 31 days were removed from analysis

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	0.405						
Dihydrocodeine	>.999	>.999					

Fentanyl	>.999	.017*	.582				
Morphine	>.999	.173	>.999	>.999			
Oxycodone	>.999	.061	>.999	>.999	>.999		
Tramadol	>.999	>.999	>.999	.088	.664	.271	
Other	>.999	>.999	>.999	.694	>.999	>.999	>.999

*p<0.05 is statistically significant

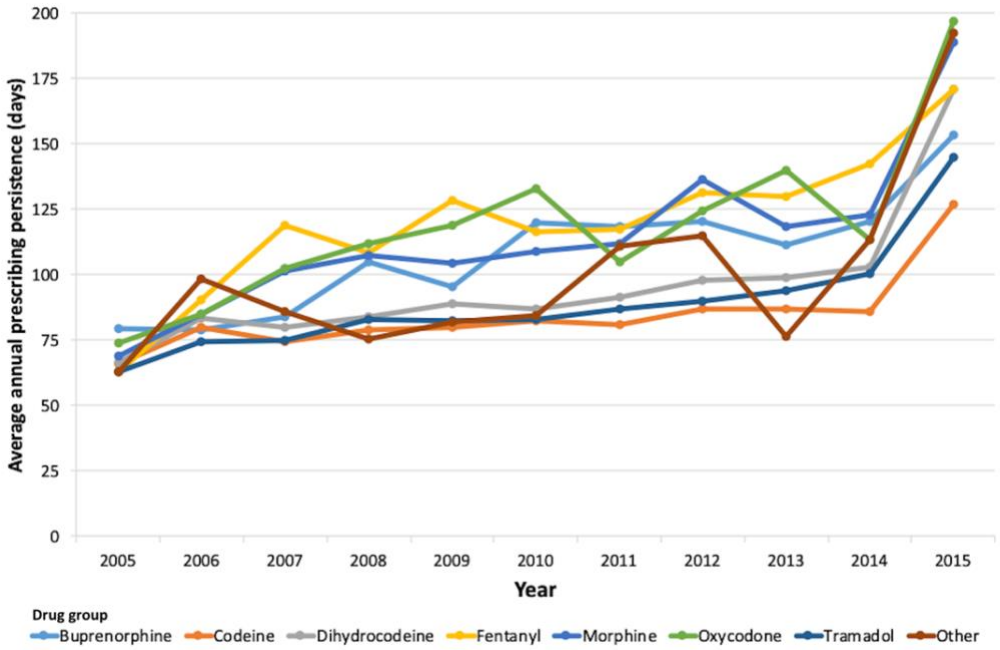


Figure G.13: Trends in average annual prescribing persistence, stratified by drug group and with >31-day repeats removed

When prescriptions which were not repeated within 31 days, were excluded from the analysis, 'other' opioids again demonstrated the largest percentage increase in average prescribing persistence between 2005 and 2015 (205.5%, from 63.1 to 192.6 days) (Figure G.13). Average prescribing persistence for each drug group, excluding single prescriptions, were significantly different ($p<0.005$, $D_{Cohen}= 1.0$, $\eta^2 =0.2$). Pairwise comparison analysis however, only confirmed that average codeine persistence was significantly less than that of fentanyl (Table G.20) ($p<0.05$). No difference was confirmed between the average durations of any other pairs of drug groups, when directly compared.

.

Table G.21: Trends in prescription persistence between 2005 and 2015, stratified by drug group

	Drug Group							
	Buprenorphine	**Codeine**	**Dihydrocodeine**	**Fentanyl**	**Morphine**	**Oxycodone**	**Tramadol**	**Other**
Mean duration (days) ±SD	14.6 ± 78.5	7.1 ± 55.0	9.4 ± 70.8	15.0 ± 90.2	19.6 ± 117.1	17.1 ± 101.0	12.0 ± 72.7	5.33 ± 49.6
2005	6.0	3.1	3.71	8.8	10.2	9.6	3.9	2.5
2015	21.7	12.0	20.0	26.6	31.4	32.5	22.0	31.6
Percentage increase (%)	262.6	288.0	438.7	203.5	208.5	240.0	468.1	1177.2
Duration without one-off doses* (days) ± SD	120.2 ± 195.5	88.9 ± 174.8	98.0 ± 209.2	129.8 ±	138.4 ± 283.9	136.4 ± 255.6	95.4 ± 185.1	87.0 ± 182.0
2005	79.4	65.9	66.3	235.8	68.9	74.0	62.7	63.1
2015	153.7	127.2	171.0	63.0	189.1	197.1	144.9	192.6
Percentage increase (%)	93.6	93.0	158.0	171.2	170.7	166.3	131.0	205.5
				171.9				
Number of events with persistence of 3 – 6 months	1 401	28 764	8 810	702	2 388	646	10 107	503
Mean ± SD	127.4 ± 90.4	2,614.9 ± 994.7	800.9 ± 98.3	63.8 ± 38.1	217.1 ± 217.6	58.7 ± 46.5	918.8 ± 423.7	45.7 ± 53.6
2005	23	1663	862	47	144	32	419	196
2015	291	5009	1049	144	763	173	1656	41
Percentage change (%)	1165.2	201.2	21.7	206.4	429.9	440.6	295.2	-79.1
Number of events with persistence more than 6 months	1,355	24,480	7,638	702	2,483	655	8,673	392
Mean ± SD	123.2 ± 95.3	2,225.5 ±	694.4 ± 240.9	63.8 ± 45.3	225.7 ± 305.4	59.6 ± 55.6	788.5 ± 493.5	35.6 ± 35.4
2005	13	1234.1	386	20	44	16	207	117
2015	320	933	1351	157	1068	204	1940	56
Rate change (%)	2361.5	5464	250.0	685.0	2327.3	1175.0	837.2	-52.1
		485.6						

*One-off doses = where consecutive prescriptions had more than 31.5 days between issues.

Table G.22: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between average prescribing persistence (days) by drug and where prescribing persistence was between 3 and 6 months

Drug	**Buprenorphine**	**Codeine**	**Dihydrocodeine**	**Fentanyl**	**Morphine**	**Oxycodone**	**Tramadol**
Codeine	<.001*						
Dihydrocodeine	0.143	>.999					
Fentanyl	>.999	<.001*	0.008*				
Morphine	>.999	0.004*	0.701	>.999			

Oxycodone	>.999	<.001*	0.002*	>.999	>.999		
Tramadol	0.110	>.999	>.999	0.006*	0.563	0.002*	
Other	>.999	<.001*	<.001*	>.999	0.563	>.999	<.001*

*p<0.05 is statistically significant

Table G.23: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between average prescribing persistence (days) by drug and where prescribing persistence was over 6 months

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	<.001*						
Dihydrocodeine	.145	>.999					
Fentanyl	>.999	<.001*	.010*				
Morphine	>.999	.005*	.708	>.999			
Oxycodone	>.999	<.001*	.004*	>.999	>.999		
Tramadol	0.116	>.999	>.999	.008*	.588	.003*	
Other	>.999	<.001*	<.001*	>.999	.569	>.999	<.001*

*p<0.05 is statistically significant

G.5.1.1 Extended durations of prescribing persistence by drug

Between 2005 and 2015, there were 53,321 prescribing events with a persistence of between 3-6 months. Occurrence of prescribing persistence between 3-6 months was highest for codeine, with a total 28,764 events. The other 7 groups of opioids had 24,557 events of 3 -6 months over the same period, around 17% fewer than for codeine alone (Table G.21). Codeine prescribing events increased by 201.2% over the study period (from 1,663 to 5,009 events per year). Tramadol was the second most prescribed opioid and had 3 times fewer events of 3-6 months than codeine, despite a 295.2% (from 419 to 1,656 events per year) increase in the number of events during the study.

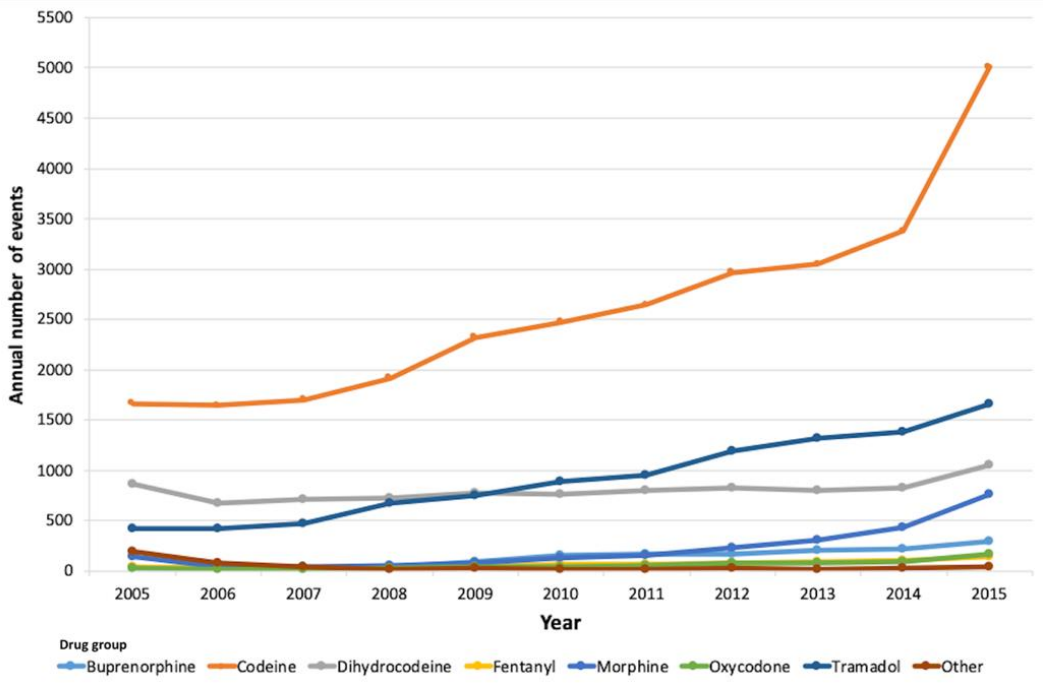


Figure G.14: Trends in prescribing persistence with duration of 3-6 months, between 2005 and 2015, stratified by drug group

Buprenorphine had the greatest percentage increase in the annual number of events of between 3-6 months (1165.2%, from 23 to 291 events per year) (Figure G.14). This was likely due to the increasing use of low-dose buprenorphine patches which are used as an alternative to codeine. Whilst morphine and oxycodone had relatively small numbers of events each year, they both had a more than 5 times increase in the number of events per year between 2005 and 2015 (429.9%, from 144 to 763 and 440.6%, from 32 to 173 events per year respectively) (Figure G.14).

Statistical analysis demonstrated a significant difference in the annual number of events with a persistence of 3-6 months between then 8 groups of opioids examined ($p<.001$, $D_{Cohen}= 3.8$, $\eta^2 =0.8$). The number of events with codeine as the last prescribed medicine, were significantly greater than for morphine, oxycodone, fentanyl, buprenorphine, and the 'other' group of opioids. Whilst

codeine events were greater in number than those for tramadol and dihydrocodeine, the difference was not significant.

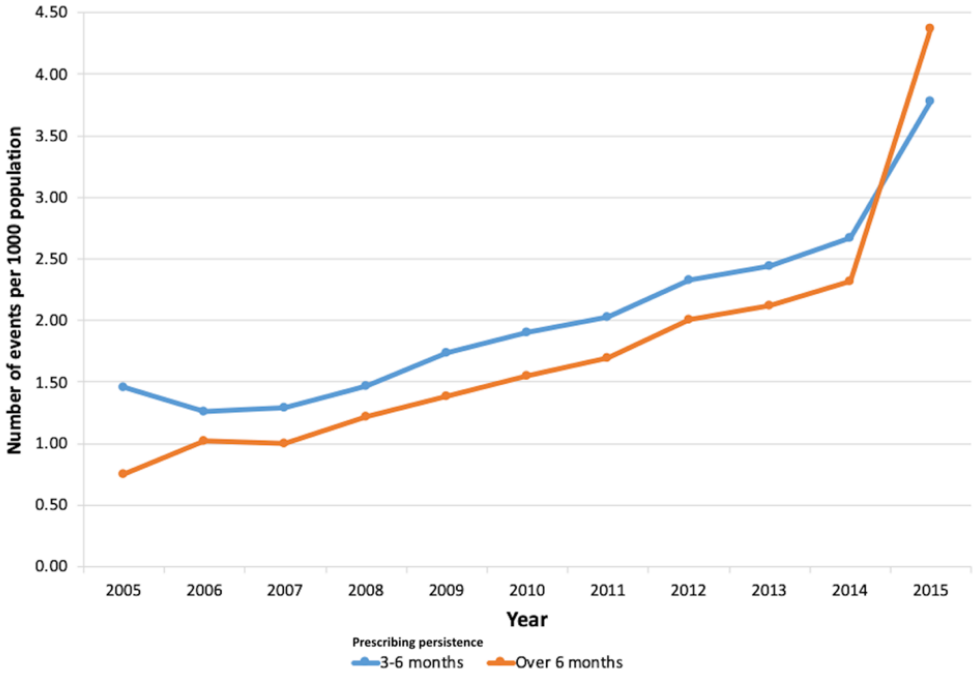


Figure-G.15: Trends in persistence of prescribing between 2005 and 2015, stratified by nominated duration

The average number of annual events with a persistence of 3-6 months for dihydrocodeine were significantly more than for oxycodone, fentanyl, and 'other' opioids, but not when compared to the other 4 groups compared. Tramadol showed the same pattern as dihydrocodeine, in terms of having significantly more events per year than oxycodone, fentanyl, and 'other' opioids, but not when compared pairwise to the other groups.

There were 15% fewer prescribing events which persisted for more than 6 months (46,378 events) than 3-6 months, during the study (Figure G.14). However, the number of events recorded in 2015 were higher for every drug group than those which persisted for 3-6 months (Table G.21). Between 2005 and 2015, the largest increases in the number of events were noted to be for strong opioids buprenorphine (2361.5%, from 13 to 320 events per year), morphine (2327.3%, from 44 to 1068 events per year) and oxycodone (1175%, from 16 to 204 events per year). Tramadol, which was noted to have a reduction in the annual number of prescriptions issued over the study period had a large increase in prescribing persistence of more than 6 months (837.2%, from 207 to 1,940 events per year).

Table G.24: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between average prescribing persistence (days) by drug and where prescribing persistence was between 3 and 6 months

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	<.001*						
Dihydrocodeine	0.143	>.999					
Fentanyl	>.999	<.001*	0.008*				
Morphine	>.999	0.004*	0.701	>.999			

Oxycodone	>.999	<.001*	0.002*	>.999	>.999		
Tramadol	0.110	>.999	>.999	0.006*	0.563	0.002*	
Other	>.999	<.001*	<.001*	>.999	0.563	>.999	<.001*

*p<0.05 is statistically significant

Table G.25: Dunn's pairwise tests with Bonferroni corrections demonstrating relationships between average prescribing persistence (days) by drug and where prescribing persistence was over 6 months

Drug	Buprenorphine	Codeine	Dihydrocodeine	Fentanyl	Morphine	Oxycodone	Tramadol
Codeine	<.001*						
Dihydrocodeine	.145	>.999					
Fentanyl	>.999	<.001*	.010*				
Morphine	>.999	.005*	.708	>.999			
Oxycodone	>.999	<.001*	.004*	>.999	>.999		
Tramadol	0.116	>.999	>.999	.008*	.588	.003*	
Other	>.999	<.001*	<.001*	>.999	.569	>.999	<.001*

*p<0.05 is statistically significant

Comparison of the annual number of events with persistence of more than 6 months (Table G.21), demonstrated a significant difference between all 8 groups of opioids examined ($p<.001$, $\eta^2 =0.8$, $D_{Cohen}= 3.5$). Pairwise comparison confirmed that codeine had significantly more events of that duration than all groups, other than dihydrocodeine and tramadol. Dihydrocodeine had significantly more events with more than 6 months duration than fentanyl , oxycodone, and the 'other' group of opioids. Tramadol showed the same pattern and had significantly more events than fentanyl, oxycodone, and 'other' opioids.

Appendix H Prescribing trends stratified by recorded diagnosis of depression and anxiety

H.1 Read codes for depression and anxiety

Table H.1: Read-codes for depression and anxiety

COND_CAT	READ_VRS	READ_CD	TERM_ID	TERM_DETAIL
DEPRESSION	3	1285	YaTgn	Family history of depression
DEPRESSION	3	1285	Ya01E	FH: Depression
DEPRESSION	3	1465	Ya04G	H/O: depression
DEPRESSION	3	62T1.	Y01Fk	Postnatal depression
DEPRESSION	3	62T1.	Y01Fl	Postpartum depression
DEPRESSION	3	62T1.	Y01Fm	Puerperal depression
DEPRESSION	3	E1120	Y01FR	Single major depressive episode, unspecified
DEPRESSION	3	E1121	Y01FS	Single major depressive episode, mild
DEPRESSION	3	E1122	Y01FT	Single major depressive episode, moderate
DEPRESSION	3	E1123	Y01FU	Single major depressive episode, severe, without mention of psychosis
DEPRESSION	3	E1124	Y01FV	Single major depressive episode, severe, with psychosis
DEPRESSION	3	E1125	Y01FW	Single major depressive episode, in partial or unspecified remission
DEPRESSION	3	E1126	Y01FX	Single major depressive episode, in full remission
DEPRESSION	3	E112z	Y01FY	Single major depressive episode NOS
DEPRESSION	3	E1130	Y01Fb	Recurrent major depressive episodes, unspecified
DEPRESSION	3	E1131	Y01Fc	Recurrent major depressive episodes, mild
DEPRESSION	3	E1132	Y01Fd	Recurrent major depressive episodes, moderate
DEPRESSION	3	E1133	Y01Fe	Recurrent major depressive episodes, severe, without mention of psychosis
DEPRESSION	3	E1134	Y01Ff	Recurrent major depressive episodes, severe, with psychosis
DEPRESSION	3	E1135	Y01Fg	Recurrent major depressive episodes, in partial or unspecified remission

DEPRESSION	3	E1136	Y01Fh	Recurrent major depressive episodes, in full remission
DEPRESSION	3	E1137	YaYAt	Recurrent depression
DEPRESSION	3	E113z	Y01Fi	Recurrent major depressive episode NOS
DEPRESSION	3	E115.	Y01Ep	Bipolar affective disorder, current episode depression
DEPRESSION	3	E1150	Y01Er	Bipolar affective disorder, currently depressed, unspecified
DEPRESSION	3	E1151	Y01Es	Bipolar affective disorder, currently depressed, mild
DEPRESSION	3	E1152	Y01Et	Bipolar affective disorder, currently depressed, moderate
DEPRESSION	3	E1153	Y01Eu	Bipolar affective disorder, currently depressed, severe, without mention of psychosis
DEPRESSION	3	E1154	Y01Ev	Bipolar affective disorder, currently depressed, severe, with psychosis
DEPRESSION	3	E1155	Y01Ew	Bipolar affective disorder, currently depressed, in partial or unspecified remission
DEPRESSION	3	E1156	Y01Ex	Bipolar affective disorder, currently depressed, in full remission
DEPRESSION	3	E115z	Y01Ey	Bipolar affective disorder, currently depressed, NOS
DEPRESSION	3	E130.	Y01FI	Psychotic reactive depression
DEPRESSION	3	E2112	YMBxo	Neurotic depression
DEPRESSION	3	E2B0.	YaYB4	Postviral depression
DEPRESSION	3	E2B1.	YaYB5	Chronic depression
DEPRESSION	3	Eu313	YMB3u	[X]Bipolar affective disorder, current episode mild or moderate depression
DEPRESSION	3	Eu314	YMB3v	[X]Bipolar affective disorder, current episode severe depression without psychotic symptoms
DEPRESSION	3	R007z	YM0wI	[D]Postoperative depression
DEPRESSION	3	X00S8	Y01Cd	Post-schizophrenic depression
DEPRESSION	3	X00Sb	Y01Gs	Anxiety depression
DEPRESSION	3	X00SQ	Y01FK	Agitated depression
DEPRESSION	3	X00SR	Y01FO	Endogenous depression
DEPRESSION	3	X00SS	Y01Fj	Endogenous depression first episode
DEPRESSION	3	X00SU	Y01Fo	Masked depression

DEPRESSION	3	X40Dl	Y418V	Mild postnatal depression
DEPRESSION	3	X40Dm	Y418Y	Severe postnatal depression
DEPRESSION	3	X40Dm	Y418Y	Severe postnatal depression
DEPRESSION	3	X7755	Y7Flu	Single stimulus depression
DEPRESSION	3	Xa11O	Y01Fn	Maternity blues
DEPRESSION	3	XaB9J	YMJar	Depression NOS
DEPRESSION	3	XaCHr	YMBxU	[X] Single episode agitated depression without psychotic symptoms
DEPRESSION	3	XaCHs	YMBxV	[X] Single episode major depression without psychotic symptoms
DEPRESSION	3	XaCIs	Yakyu	[X]Mild depression
DEPRESSION	3	XaCIs	Yabyn	Mild depression
DEPRESSION	3	XaCIt	Yabyo	Moderate depression
DEPRESSION	3	XaCIu	Yabyq	Severe depression
DEPRESSION	3	XaImU	YalJv	Symptoms of depression
DEPRESSION	3	XaK6d	YanJb	Depression annual review
DEPRESSION	3	XaK6e	YanJc	Depression medication review
DEPRESSION	3	XaLG0	YaoJo	Depression resolved
DEPRESSION	3	XaNg1	Yaqge	History of postnatal depression
DEPRESSION	3	XaX0C	Yattn	Suspected depression
DEPRESSION	3	XaX53	Yatxk	Single major depressive episode, severe, with psychosis, psychosis in remission
DEPRESSION	3	XaX54	Yatxl	Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
DEPRESSION	3	XaY2C	Yaudm	Antenatal depression
DEPRESSION	3	XE1Y0	Y01FQ	Single major depressive episode
DEPRESSION	3	XE1YC	Y01FM	Neurotic depression reactive type
DEPRESSION	3	XE1YC	Y01FL	Reactive depression
DEPRESSION	3	XE1Zb	YMBxa	[X] Depression NOS

DEPRESSION	3	XM1GC	Y01FZ	Endogenous depression - recurrent
DEPRESSION	3	XSEGJ	YSNUF	Major depression
DEPRESSION	3	XSGok	YSRJY	Mild major depression
DEPRESSION	3	XSGol	YSRJZ	Moderate major depression
DEPRESSION	3	XSGom	YSRJa	Severe major depression without psychotic features
DEPRESSION	3	XSGon	Yat7Y	[X]Major depression, severe with psychotic symptoms
DEPRESSION	3	XSGon	YSRJc	Psychotic depression
DEPRESSION	3	XSGon	YSRJb	Severe major depression with psychotic features
DEPRESSION	3	XSKr7	YamzO	Cotard syndrome
DEPRESSION	3	ZV790	Ya0qU	[V]Screening for depression
DEPRESSION	2	1285	0	FH: Depression
DEPRESSION	2	1287	0	FH: Manic depressive state
DEPRESSION	2	1465	0	H/O: depression
DEPRESSION	2	1B1U.	0	Symptoms of depression
DEPRESSION	2	1JJ..	0	Suspected depression
DEPRESSION	2	212S.	0	Depression resolved
DEPRESSION	2	9H90.	0	Depression annual review
DEPRESSION	2	9H91.	0	Depression medication review
DEPRESSION	2	9H92.	0	Depression interim review
DEPRESSION	2	9HA0.	0	On depression register
DEPRESSION	2	E112.	13	Endogenous depression first episode
DEPRESSION	2	E1120	0	Single major depressive episode, unspecified
DEPRESSION	2	E1121	0	Single major depressive episode, mild
DEPRESSION	2	E1122	0	Single major depressive episode, moderate
DEPRESSION	2	E1123	0	Single major depressive episode, severe, without mention of psychosis

DEPRESSION	2	E1124	0	Single major depressive episode, severe, with psychosis
DEPRESSION	2	E1125	0	Single major depressive episode, in partial or unspecified remission
DEPRESSION	2	E1126	0	Single major depressive episode, in full remission
DEPRESSION	2	E112z	0	Single major depressive episode NOS
DEPRESSION	2	E113.	11	Endogenous depression - recurrent
DEPRESSION	2	E1130	0	Recurrent major depressive episodes, unspecified
DEPRESSION	2	E1131	0	Recurrent major depressive episodes, mild
DEPRESSION	2	E1132	0	Recurrent major depressive episodes, moderate
DEPRESSION	2	E1133	0	Recurrent major depressive episodes, severe, without mention of psychosis
DEPRESSION	2	E1134	0	Recurrent major depressive episodes, severe, with psychosis
DEPRESSION	2	E1135	0	Recurrent major depressive episodes, in partial or unspecified remission
DEPRESSION	2	E1136	0	Recurrent major depressive episodes, in full remission
DEPRESSION	2	E1137	0	Recurrent depression
DEPRESSION	2	E113z	0	Recurrent major depressive episode NOS
DEPRESSION	2	E115.	11	Manic-depressive - now depressed
DEPRESSION	2	E1150	0	Bipolar affective disorder, currently depressed, unspecified
DEPRESSION	2	E1151	0	Bipolar affective disorder, currently depressed, mild
DEPRESSION	2	E1152	0	Bipolar affective disorder, currently depressed, moderate
DEPRESSION	2	E1153	0	Bipolar affective disorder, currently depressed, severe, without mention of psychosis
DEPRESSION	2	E1154	0	Bipolar affective disorder, currently depressed, severe, with psychosis
DEPRESSION	2	E1155	0	Bipolar affective disorder, currently depressed, in partial or unspecified remission
DEPRESSION	2	E1156	0	Bipolar affective disorder, currently depressed, in full remission
DEPRESSION	2	E115z	0	Bipolar affective disorder, currently depressed, NOS
DEPRESSION	2	E11z2	0	Masked depression
DEPRESSION	2	E130.	11	Psychotic reactive depression

DEPRESSION	2	E135.	0	Agitated depression
DEPRESSION	2	E2003	0	Anxiety with depression
DEPRESSION	2	E204.	11	Postnatal depression
DEPRESSION	2	E204.	0	Neurotic depression reactive type
DEPRESSION	2	E2B0.	0	Postviral depression
DEPRESSION	2	E2B1.	0	Chronic depression
DEPRESSION	2	Eu204	0	[X]Post-schizophrenic depression
DEPRESSION	2	Eu32.	13	[X]Single episode of reactive depression
DEPRESSION	2	Eu32.	12	[X]Single episode of psychogenic depression
DEPRESSION	2	Eu320	0	[X]Mild depressive episode
DEPRESSION	2	Eu321	0	[X]Moderate depressive episode
DEPRESSION	2	Eu322	0	[X]Severe depressive episode without psychotic symptoms
DEPRESSION	2	Eu323	0	[X]Severe depressive episode with psychotic symptoms
DEPRESSION	2	Eu324	0	[X]Mild depression
DEPRESSION	2	Eu325	0	[X]Major depression, mild
DEPRESSION	2	Eu326	0	[X]Major depression, moderately severe
DEPRESSION	2	Eu327	0	[X]Major depression, severe without psychotic symptoms
DEPRESSION	2	Eu328	0	[X]Major depression, severe with psychotic symptoms
DEPRESSION	2	Eu329	0	[X]Single major depressive episode, severe, with psychosis, psychosis in remission
DEPRESSION	2	Eu32A	0	[X]Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
DEPRESSION	2	Eu32B	0	[X]Antenatal depression
DEPRESSION	2	Eu32y	0	[X]Other depressive episodes
DEPRESSION	2	Eu32z	11	[X]Depression NOS
DEPRESSION	2	Eu32z	14	[X] Reactive depression NOS
DEPRESSION	2	Eu32z	0	[X]Depressive episode, unspecified

DEPRESSION	2	Eu32z	0	[X]Depressive episode, unspecified
DEPRESSION	2	Eu33.	13	[X]Recurrent episodes of reactive depression
DEPRESSION	2	Eu330	0	[X]Recurrent depressive disorder, current episode mild
DEPRESSION	2	Eu331	0	[X]Recurrent depressive disorder, current episode moderate
DEPRESSION	2	Eu332	0	[X]Recurrent depressive disorder, current episode severe without psychotic symptoms
DEPRESSION	2	Eu333	0	[X]Recurrent depressive disorder, current episode severe with psychotic symptoms
DEPRESSION	2	Eu334	0	[X]Recurrent depressive disorder, currently in remission
DEPRESSION	2	Eu33y	0	[X]Other recurrent depressive disorders
DEPRESSION	2	Eu33z	0	[X]Recurrent depressive disorder, unspecified
DEPRESSION	2	Eu341	13	[X]Neurotic depression
DEPRESSION	2	Eu341	14	[X]Persistant anxiety depression
DEPRESSION	2	Eu412	11	[X]Mild anxiety depression
DEPRESSION	2	Eu530	11	[X]Postnatal depression NOS
DEPRESSION	2	Eu530	12	[X]Postpartum depression NOS
DEPRESSION	2	R007z	13	[D]Postoperative depression
DEPRESSION	2	ZV790	0	[V]Screening for depression
ANXIETY	3	1B1..	Y7D89	General nervous symptoms
ANXIETY	3	1B1Z.	Y7D86	General nervous symptom NOS
ANXIETY	3	E200.	Y01GY	Anxiety disorder
ANXIETY	3	E200.	Y01Gq	Anxiety state
ANXIETY	3	E2000	Y01Gb	Anxiety state unspecified
ANXIETY	3	E2002	Y01Gp	Anxiety neurosis
ANXIETY	3	E2002	Y01Gm	GAD - Generalised anxiety disorder
ANXIETY	3	E2002	Y01Gl	Generalised anxiety disorder
ANXIETY	3	E2004	YaYAu	Chronic anxiety

ANXIETY	3	E2005	YaYAv	Recurrent anxiety
ANXIETY	3	E200z	Y01Ga	Anxiety state NOS
ANXIETY	3	E2020	Y01GH	Phobia unspecified
ANXIETY	3	E2021	Y01GL	Agoraphobia with panic attacks
ANXIETY	3	E2022	Y01GK	Agoraphobia without mention of panic attacks
ANXIETY	3	E2023	Y01GQ	Social phobia, fear of eating in public
ANXIETY	3	E2024	Y01GP	Social phobia, fear of public speaking
ANXIETY	3	E2025	Y01GO	Social phobia, fear of public washing
ANXIETY	3	E2026	Y01GG	Acrophobia
ANXIETY	3	E2027	Y01GS	Animal phobia
ANXIETY	3	E2028	Y01GT	Claustrophobia
ANXIETY	3	E2029	Y01GF	Fear of crowds
ANXIETY	3	E202C	YaYAy	Dental phobia
ANXIETY	3	E202E	YaYB0	Fear of pregnancy
ANXIETY	3	E2920	YM1hy	Separation anxiety disorder
ANXIETY	3	Eu40y	YMB4V	[X]Other phobic anxiety disorders
ANXIETY	3	Eu410	YMB4Y	[X]Panic disorder [episodic paroxysmal anxiety]
ANXIETY	3	Ua1qa	YMGBQ	Fear of dentist
ANXIETY	3	Ua1qc	YMGBS	Fear of not coping with treatment
ANXIETY	3	Ua1qd	YMGBT	Fear of lifts
ANXIETY	3	Ua1qe	YMGBU	Fear of thunderstorm
ANXIETY	3	Ua1qf	YMGWS	Terrified
ANXIETY	3	Ua1qo	Ya5FV	Anxiety about making mistakes
ANXIETY	3	Ua1qp	Ya5FU	Anxiety about altered body image
ANXIETY	3	Ua1qs	YMGBi	Fear of wetting self in public

ANXIETY	3	Ua1qS	YMGBI	Panic attack
ANXIETY	3	Ua1qt	YMGBj	Fear of losing control of bowels in public
ANXIETY	3	Ua1qU	YMGBK	Fear of walking
ANXIETY	3	Ua1qV	YMGBL	Fear of mobilising
ANXIETY	3	Ua1qW	YMGBM	Fear of disconnection from ventilator
ANXIETY	3	Ua1qX	YMGBN	Fear of being left alone during period of dependence
ANXIETY	3	Ua1qY	YMGBO	Fear of being left alone
ANXIETY	3	X00RP	Y017s	Organic anxiety disorder
ANXIETY	3	X00Sa	Y01Gi	Non-situational panic attack
ANXIETY	3	X00Sb	Y01Gr	Mixed anxiety and depressive disorder
ANXIETY	3	X00Sc	Y01Gt	Anxiety hysteria
ANXIETY	3	X00Sd	Y01H8	Stage fright
ANXIETY	3	X00Se	Y01H9	Examination fear
ANXIETY	3	X00Se	Y01H9	Examination fear
ANXIETY	3	X00SV	Y01GI	Agoraphobia
ANXIETY	3	X00SW	Y01GM	Social phobia
ANXIETY	3	X00SX	Ya0so	Specific phobia
ANXIETY	3	X00SY	Y01GU	Needle phobia
ANXIETY	3	X00SZ	Y01Gh	Situational panic attack
ANXIETY	3	X761a	Y7D8Q	Fear of swallowing
ANXIETY	3	X761b	Y7D8R	Fear of collapsing
ANXIETY	3	X761c	Y7D8S	Fear of fainting
ANXIETY	3	X761d	Y7D8T	Fear of having a heart attack
ANXIETY	3	X761e	Y7D8U	Fear of shaking
ANXIETY	3	X761f	Y7D8V	Fear of sweating

ANXIETY	3	X761g	Y7D8W	Fear of dying
ANXIETY	3	X761h	Y7D8X	Fear of going crazy
ANXIETY	3	X761i	Y7D8a	Fear of losing emotional control
ANXIETY	3	X761j	Y7D8b	Fear of becoming fat
ANXIETY	3	X761l	Y7D8f	Fear of appearing ridiculous
ANXIETY	3	X761m	Y7D8g	Fear of saying the wrong thing
ANXIETY	3	X761N	Y7D7s	Anxiety and fear
ANXIETY	3	X761n	Y7D8m	Fear of going out
ANXIETY	3	X761p	Y7D8p	Fear of empty streets
ANXIETY	3	X761P	Y7D8A	Ill-at-ease
ANXIETY	3	X761q	Y7D8q	Fear of open spaces
ANXIETY	3	X761r	Y7D8r	Fear of crossing streets
ANXIETY	3	X761T	Y7D8J	Anxiety about health
ANXIETY	3	X761t	Y7D8t	Fear of transport
ANXIETY	3	X761U	Y7D8K	Fear of losing control of bowels
ANXIETY	3	X761u	Y7D8x	Social fear
ANXIETY	3	X761v	Y7D8y	Fear of activities in public
ANXIETY	3	X761V	Y7D8L	Fear of wetting self
ANXIETY	3	X761w	Y7D8z	Fear of eating in public
ANXIETY	3	X761W	Y7D8M	Fear of vomiting in public
ANXIETY	3	X761X	Y7D8N	Fear of having a fit
ANXIETY	3	X761x	Y7D90	Fear of public speaking
ANXIETY	3	X761Y	Y7D8O	Fear of choking
ANXIETY	3	X761Y	Y7D8O	Fear of choking
ANXIETY	3	X761y	Y7D91	Fear of using public toilets

ANXIETY	3	X761Z	Ya1tE	Anxiety about blushing
ANXIETY	3	X761z	Y7D92	Fear of writing in public
ANXIETY	3	X7620	Y7D93	Fear of social group activities
ANXIETY	3	X7621	Y7D94	Fear of being in a small group
ANXIETY	3	X7622	Y7D95	Fear of social gatherings
ANXIETY	3	X7623	Y7D96	Fear of speaking on the phone
ANXIETY	3	X7624	Y7D97	Fear of speaking to people in authority
ANXIETY	3	X7625	Y7D98	Fear of being laughed at
ANXIETY	3	X7626	Y7D99	Fear of being watched
ANXIETY	3	X7627	Ya0sq	Specific fear
ANXIETY	3	X7628	Y7D9B	Fear of natural phenomena
ANXIETY	3	X7629	Y7D9C	Fear of the dark
ANXIETY	3	X762A	Y7D9D	Fear of animals
ANXIETY	3	X762a	Y7D9f	Fear of ghosts
ANXIETY	3	X762B	Y7D9E	Fear of feathers
ANXIETY	3	X762b	Y7D9g	Fear of school
ANXIETY	3	X762C	Y7D9F	Fear of enclosed spaces
ANXIETY	3	X762E	Y7D9H	Fear of tunnels
ANXIETY	3	X762F	Y7D9I	Fear of phone boxes
ANXIETY	3	X762G	Y7D9J	Fear of flying
ANXIETY	3	X762H	Y7D9K	Flying phobia
ANXIETY	3	X762I	Y7D9L	Fear associated with illness and body function
ANXIETY	3	X762J	Y7D9M	Fear of anaesthetic
ANXIETY	3	X762K	Y7D9N	Fear of general anaesthetic
ANXIETY	3	X762L	Y7D9P	Fear of awareness under general anaesthetic

ANXIETY	3	X762M	Y7D9Q	Fear of not waking from general anaesthetic
ANXIETY	3	X762N	Y7D9R	Fear of local anaesthetic
ANXIETY	3	X762O	Y7D9S	Fear of problem after anaesthetic
ANXIETY	3	X762R	Ya5sS	Fear of surgical masks
ANXIETY	3	X762S	Y7D9X	Fear of hospitals
ANXIETY	3	X762T	Y7D9Y	Fear of death
ANXIETY	3	X762U	Y7D9Z	Fear of contracting disease
ANXIETY	3	X762V	Y7D9a	Fear of infection
ANXIETY	3	X762W	Y7D9b	Fear of contracting venereal disease
ANXIETY	3	X762X	Y7D9c	Fear of contracting HIV infection
ANXIETY	3	X762Y	Y7D9d	Fear of contracting radiation sickness
ANXIETY	3	X762Z	Y7D9e	Fear of the bogey man
ANXIETY	3	X78wp	Y7KRx	Apprehension
ANXIETY	3	Xa00r	Ya0ss	Fear of heights
ANXIETY	3	Xa00s	Ya0st	Fear of water
ANXIETY	3	Xa0XB	Ya1lw	Fear relating to body function
ANXIETY	3	Xa0XG	Ya1m3	Anxiety about losing control of bowels
ANXIETY	3	Xa0XH	Ya1m4	Anxiety about wetting self
ANXIETY	3	Xa0XI	Ya1m5	Anxiety about vomiting in public
ANXIETY	3	Xa0XJ	Ya1m6	Anxiety about having a fit
ANXIETY	3	Xa0XK	Ya1m7	Anxiety about choking
ANXIETY	3	Xa0XK	Ya1m7	Anxiety about choking
ANXIETY	3	Xa0XM	Ya1m9	Anxiety about swallowing
ANXIETY	3	Xa0XN	Ya1mA	Anxiety about collapsing
ANXIETY	3	Xa0XO	Ya1mB	Anxiety about shaking

ANXIETY	3	Xa0XP	Ya1mC	Anxiety about sweating
ANXIETY	3	Xa0XQ	Ya1mD	Anxiety about dying
ANXIETY	3	Xa0XR	Ya1mF	Anxiety about going crazy
ANXIETY	3	Xa0XU	Ya1mK	Anxiety about becoming fat
ANXIETY	3	Xa0XU	Ya1mL	Anxiety about obesity
ANXIETY	3	Xa0XX	Ya1mO	Anxiety about fainting
ANXIETY	3	Xa0XX	Ya1mO	Anxiety about fainting
ANXIETY	3	Xa0XY	Ya1mP	Anxiety about having a heart attack
ANXIETY	3	Xa19B	Ya2g2	Performance anxiety
ANXIETY	3	Xa1a8	Ya3Bh	Examination phobia
ANXIETY	3	Xa1Ev	Y7D9V	Fear of needles
ANXIETY	3	Xa3Vj	Ya5rp	Panic
ANXIETY	3	Xa3Vk	Ya5rq	Fear of insects
ANXIETY	3	Xa3Vl	Ya5rr	Fear of birds
ANXIETY	3	Xa3WH	Ya5sR	Fear associated with healthcare
ANXIETY	3	Xa3WI	Ya5sT	Fear of blood
ANXIETY	3	Xa3WJ	Ya5sU	Fear of getting cancer
ANXIETY	3	Xa3Xk	Ya5up	Level of anxiety
ANXIETY	3	Xa7k9	YaV9p	Parental anxiety
ANXIETY	3	Xa7kB	YaV9s	Anxiety attack
ANXIETY	3	Xa7kB	YaV9s	Anxiety attack
ANXIETY	3	Xa7lj	YaVCF	Cancer phobia
ANXIETY	3	Xa7lx	YaVCT	Pre-examination nerves
ANXIETY	3	XaA5Z	YaYts	Beck anxiety inventory
ANXIETY	3	Xaafv	YawVM	Anxiety about breathlessness

ANXIETY	3	XaB96	Ya6jS	Other phobias
ANXIETY	3	XaEG0	Y50cm	Dysmorphophobia
ANXIETY	3	XaIvf	Yalgc	Fear of falling
ANXIETY	3	XaMFU	YapP5	Paruresis
ANXIETY	3	XaP8d	Yarkm	Stranger anxiety
ANXIETY	3	XaZJQ	YavR8	Generalised anxiety disorder 2 scale
ANXIETY	3	XE0ra	Y7D7x	Nervousness
ANXIETY	3	XE0rb	Ya5b6	Anxiety
ANXIETY	3	XE0ri	Y7D8h	Fear
ANXIETY	3	XE1Y7	Y01Gd	Episodic paroxysmal anxiety disorder
ANXIETY	3	XE1Y7	Y01Gc	Panic disorder
ANXIETY	3	XE1YA	Ya5am	Phobic anxiety disorder
ANXIETY	3	XE1YB	Y01GE	Phobic disorder NOS
ANXIETY	3	XE2Po	Y7DgD	Maternal concern
ANXIETY	3	XM00G	Y7D8C	Separation anxiety
ANXIETY	3	XM0Ak	Y01GV	School phobia
ANXIETY	3	XM0eK	YM9X5	Hospital anxiety and depression scale
ANXIETY	3	XM1OD	Y71RO	Hydrophobia
ANXIETY	2	ZV655	0	[V]Person with feared complaint, no diagnosis made
ANXIETY	2	1288	0	FH: Anxiety state
ANXIETY	2	1466	0	H/O: anxiety state
ANXIETY	2	173f.	0	Anxiety about breathlessness
ANXIETY	2	1B1H.	11	Fear
ANXIETY	2	1Bb..	0	Specific fear
ANXIETY	2	1Bb0.	0	Fear of falling

ANXIETY	2	1Bb1.	0	Fear of getting cancer
ANXIETY	2	1M61.	0	Fearful with pain
ANXIETY	2	225K.	0	O/E - fearful mood
ANXIETY	2	E200.	0	Anxiety states
ANXIETY	2	E2000	0	Anxiety state unspecified
ANXIETY	2	E2001	0	Panic disorder
ANXIETY	2	E2002	0	Generalised anxiety disorder
ANXIETY	2	E2003	0	Anxiety with depression
ANXIETY	2	E2004	0	Chronic anxiety
ANXIETY	2	E2005	0	Recurrent anxiety
ANXIETY	2	E200z	0	Anxiety state NOS
ANXIETY	2	E202.	12	Phobic anxiety
ANXIETY	2	E2020	0	Phobia unspecified
ANXIETY	2	E2021	0	Agoraphobia with panic attacks
ANXIETY	2	E2022	0	Agoraphobia without mention of panic attacks
ANXIETY	2	E2023	0	Social phobia, fear of eating in public
ANXIETY	2	E2024	0	Social phobia, fear of public speaking
ANXIETY	2	E2025	0	Social phobia, fear of public washing
ANXIETY	2	E2026	0	Acrophobia
ANXIETY	2	E2027	0	Animal phobia
ANXIETY	2	E2028	0	Claustrophobia
ANXIETY	2	E2029	0	Fear of crowds
ANXIETY	2	E202A	0	Fear of flying
ANXIETY	2	E202B	0	Cancer phobia
ANXIETY	2	E202C	0	Dental phobia
ANXIETY	2	E202D	0	Fear of death
ANXIETY	2	E202E	0	Fear of pregnancy
ANXIETY	2	E202z	0	Phobic disorder NOS

ANXIETY	2	E227z	11	Fear of ejaculation
ANXIETY	2	Eu054	0	[X]Organic anxiety disorder
ANXIETY	2	Eu341	14	[X]Persistent anxiety depression
ANXIETY	2	Eu40.	0	[X]Phobic anxiety disorders
ANXIETY	2	Eu400	0	[X]Agoraphobia
ANXIETY	2	Eu401	0	[X]Social phobias
ANXIETY	2	Eu402	0	[X]Specific (isolated) phobias
ANXIETY	2	Eu403	0	[X]Needle phobia
ANXIETY	2	Eu40y	0	[X]Other phobic anxiety disorders
ANXIETY	2	Eu40z	0	[X]Phobic anxiety disorder, unspecified
ANXIETY	2	Eu41.	0	[X]Other anxiety disorders
ANXIETY	2	Eu410	0	[X]Panic disorder [episodic paroxysmal anxiety]
ANXIETY	2	Eu411	0	[X]Generalized anxiety disorder
ANXIETY	2	Eu411	0	[X]Generalized anxiety disorder
ANXIETY	2	Eu412	0	[X]Mixed anxiety and depressive disorder
ANXIETY	2	Eu413	0	[X]Other mixed anxiety disorders
ANXIETY	2	Eu41y	0	[X]Other specified anxiety disorders
ANXIETY	2	Eu41z	0	[X]Anxiety disorder, unspecified
ANXIETY	2	Eu515	11	[X]Dream anxiety disorder
ANXIETY	2	Eu931	0	[X]Phobic anxiety disorder of childhood
ANXIETY	2	Eu932	0	[X]Social anxiety disorder of childhood

H.2 Results

In the eleven years of the study, the SAIL databank registered 475,085 individuals (aged >18 years) with a recorded diagnosis of depression or anxiety. When examined by more precise diagnosis, 275,232 (57.9%) people had a recorded diagnosis of anxiety and 354,292 (74.6%) a recorded diagnosis of depression, revealing a large cross-over in diagnosis.

H.2.1 Trends in the number of people receiving prescriptions

Over the 11 years of the study, opioid prescriptions were issued to a total of 277,988 (n= 1,099,026) people who also had a recorded diagnosis of depression and/or anxiety (RDDA) and no recorded diagnosis of cancer. Consequently, 58.5% of people with an RDDA recorded in the SAIL databank, received prescriptions for opioids between 2005 and 2015.

People with an RDDA equated to 25.3% of all people with a non-cancer diagnosis who received opioid prescriptions. A Mann-Whitney U tests indicated there was a significant difference between the number of people receiving opioid prescriptions who had a recorded diagnosis of depression and/or anxiety and those without, (U=<.001, p<.001, r=0.8). The median number of people with an RDDA was 44.4 people per 1000 population and 104.3 people per 1000 population for those without.

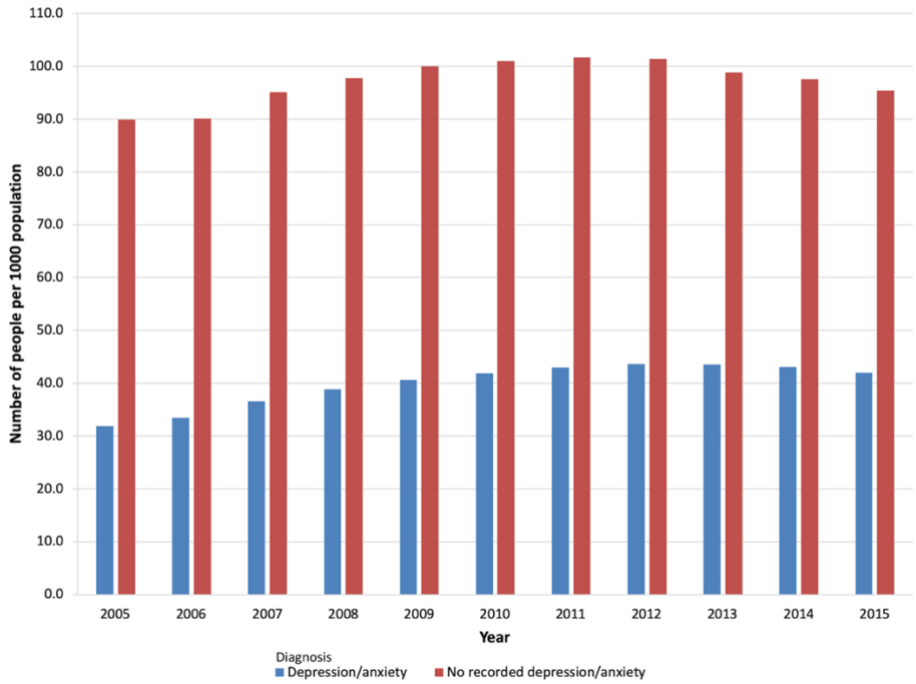


Figure H.1: Trends in the number of people per 1000 population, receiving prescriptions for opioids and with or without a recorded diagnosis of depression and/or anxiety

Annual trends demonstrated that percentage increases in the number of people receiving opioid prescriptions who also had an RDDA were much greater than the number of people without an RDDA (Table H.2).

Table H.2: Annual trends in the number of people receiving opioid prescriptions with or without a recorded diagnosis of depression and/or anxiety. Data adjusted to number per 1000 population

	People per 1000 population receiving opioid prescriptions					
	No recorded diagnosis of depression/anxiety			Recorded diagnosis of depression/anxiety		
	Weak opioid	Strong opioid	Total	Weak opioid	Strong opioid	Total
2005	89.9	3.3	93.2	31.8	1.2	33.0
2015	95.4	8.3	103.6	42.0	5.0	47.0
Percentage change (%) 2005-2015	6.1	153.1	11.2	31.8	332.5	42.4

Whilst there were 2.8 times more people without an RDDA receiving opioid prescriptions in 2005 compared to those with an RDDA; the annual number of people increased 3.8 times more in the latter group. By 2015, there were 2.2 times more people without an RDDA, receiving opioid prescriptions compared to those with that diagnosis.

In 2005, 3.5% (3.3 people per 1000 population, n=93.2 people per 1000 population) of all people receiving opioid prescriptions and whom did not have an RDDA, received strong opioid prescriptions. There was a 153.1% increase (from 3.3 to 8.3 people per 1000 population) in the annual number of people receiving strong opioid prescriptions resulting in 8.0% (8.3 people per 1000 population, n=103.6 people per 1000 population) of all people in that category receiving strong opioids in 2015 (Table H.2).

There was a total of 27,358 (30.4%, n=89,989) people who received strong opioid prescriptions over the study period and also had RDDA on their medical record. There was a significant difference (U=13.0, p=.001, r=0.5) in the number of people receiving strong opioid prescriptions who had an RDDA (median=2.5 people per 1000 population) and those without (median=4.7 people per 1000 population). Whilst statistically significant, the effect size was moderate.

The percentage of people with an RDDA and receiving a prescription for a strong opioid as a total of all people with that diagnosis receiving opioid prescriptions, was 3.6% in 2005. The annual number of people in that category increased 332.5% over the 11 years of the study, resulting in 10.6% (5.0 people per 1000 population, n=47.0 people per 1000 population) of the annual number of people with an RDDA receiving prescriptions for strong opioids in 2015 (Table H.2).

Over the 11 years examined, 29.1% of people receiving prescriptions for weak opioids had a recorded diagnosis of depression and/or anxiety. The annual number of people receiving weak opioid prescriptions increased by 31.8% (from 31.8 to 42.0 people per 1000 population) over the study period when there was also an RDDA (Table H.2: Annual trends in the number of people receiving opioid prescriptions with or without a recorded diagnosis of depression and/or anxiety. Data adjusted to number per 1000 population). This compared to 6.1% (from 89.9 to 95.4 people per 1000 population) where there was not an RDDA.

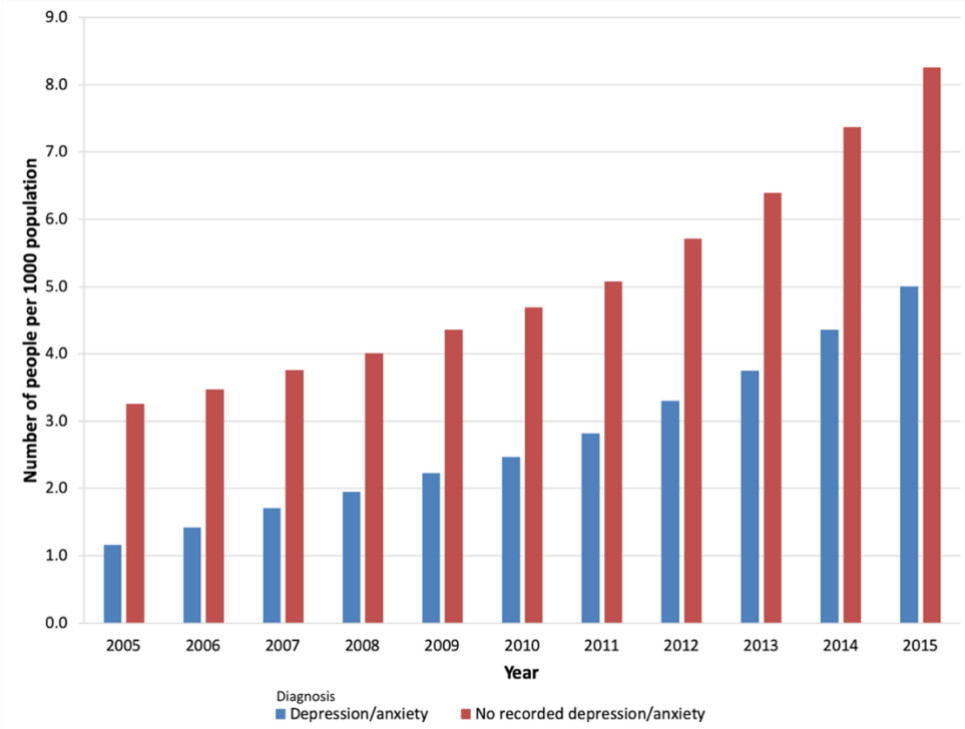


Figure H.2: Trends in the annual number of people per 1000 population receiving strong opioid prescriptions and whether they have a recorded diagnosis of depression and/or anxiety

Weak opioid prescriptions were issued to a total of 276,403 (25.4%, n=1,089,618) people with RDDA. The median number of people receiving prescriptions for weak opioids without an RDDA was 97.8 people per 1000 population and 41.9 people per 1000 population for those with an RDDA. A Mann-Whitney U test demonstrated the difference in the numbers of people receiving weak opioids, with or without an RDDA was significant, U=<.001, p<.001, r=0.8.

The number of people without an RDDA and receiving weak opioids was 2.8 times higher than those with that diagnosis in 2005 (89.9 versus 31.8 people per 1000 population respectively) and changed to a 2.2 times difference by 2015 (95.4 versus 42.0 people per 1000 population). Weak opioid prescriptions and co-diagnoses of depression/anxiety accounted for 26.2% (31.8 people per 1000 population, n=121.8) of all weak opioid prescriptions at the start of the study. By 2015, the percentage of the annual number of people receiving weak opioid prescriptions who also had an RDDA had risen to 30.6% (42.0 people per 1000 population, n= 137.4).

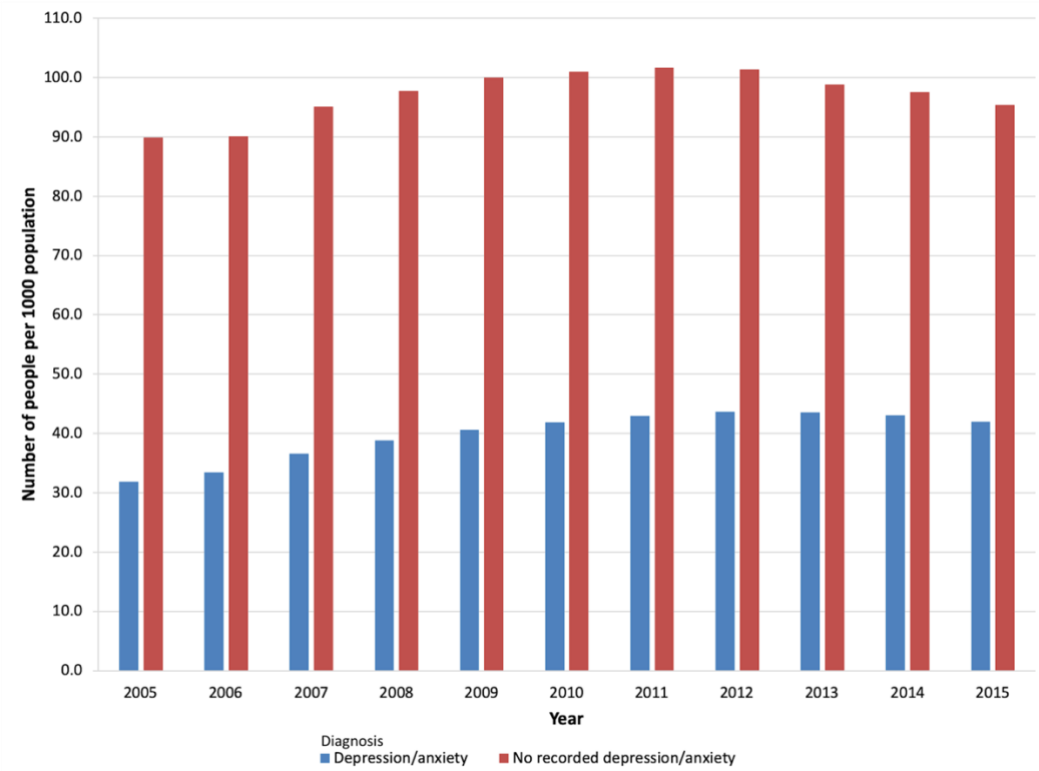


Figure H.3: Annual number of people per 1000 population receiving weak opioid prescriptions and whether they have a recorded diagnosis of depression and/or anxiety

H.2.2 Trends in the number of prescriptions

There was a total of 7,466,357 (n = 22,786.565) prescriptions for opioid medicines issued to people with a recorded diagnosis of depression and/or anxiety (RDDA) but no diagnosis of cancer (non-cancer). Prescriptions for opioid medicines for people with a recorded diagnosis of depression and/or anxiety comprised 32.7% (3140.0 of 9593.3 prescriptions per 1000 people) of all the opioid prescriptions issued across the 11 years of the study. The difference between the number of prescriptions for people with an RDDA (median=290.8 prescriptions per 1000 population) and those without (median=597.4 prescriptions per 1000 population), was determined significant by a Mann-Whitney U test (U=<.001, p<.001, r=0.8).

Strong opioid prescriptions for people with an RDDA comprised 4.4% (997,749) of the total of all opioid prescriptions issued and 41% (n = 2,436,171) of the total of strong opioid prescriptions being prescribed. Prescriptions for weak opioids issued to people with an RDDA equated to 28.4% (6,468,608) of all opioids prescribed and 32% (n = 20,350,394) of the total of weak opioids prescribed in the 11 years examined.

Table H.3: Annual trends in the number of opioid prescriptions with or without a recorded diagnosis of depression and/or anxiety. Data adjusted to number per 1000 sex-adjusted population

	Prescriptions per 1000 population receiving opioid prescriptions	
	No recorded diagnosis of depression/anxiety	Recorded diagnosis of depression/anxiety

	Weak opioid	Strong opioid	Total	Weak opioid	Strong opioid	Total
2005	480.4	27.6	508.0	176.3	12.6	188.8
2015	547.5	90.9	638.5	290.1	72.2	362.2
Percentage change (%) 2005-2015	14.0	229.6	25.7	64.6	474.3	91.8

The annual number of prescriptions for people with an RDDA increased 91.8% (from 188.8 to 362.2 prescriptions per 1000 population) between 2005 and 2015. The number of prescriptions issued to people without an RDDA increased by 25.7% (from 508.0 to 638.5 prescriptions per 1000 population) although there were 2.1 times more prescriptions issued to people without depression or anxiety over the 11 years examined. In 2005, 2.7 times more prescriptions were issued to people without an RDDA compared to those with (508.0 versus 188.8 prescriptions per 1000 people respectively). This changed to a 1.8 times difference (638.5 versus 362.2 prescriptions per 1000 people respectively) in 2015.

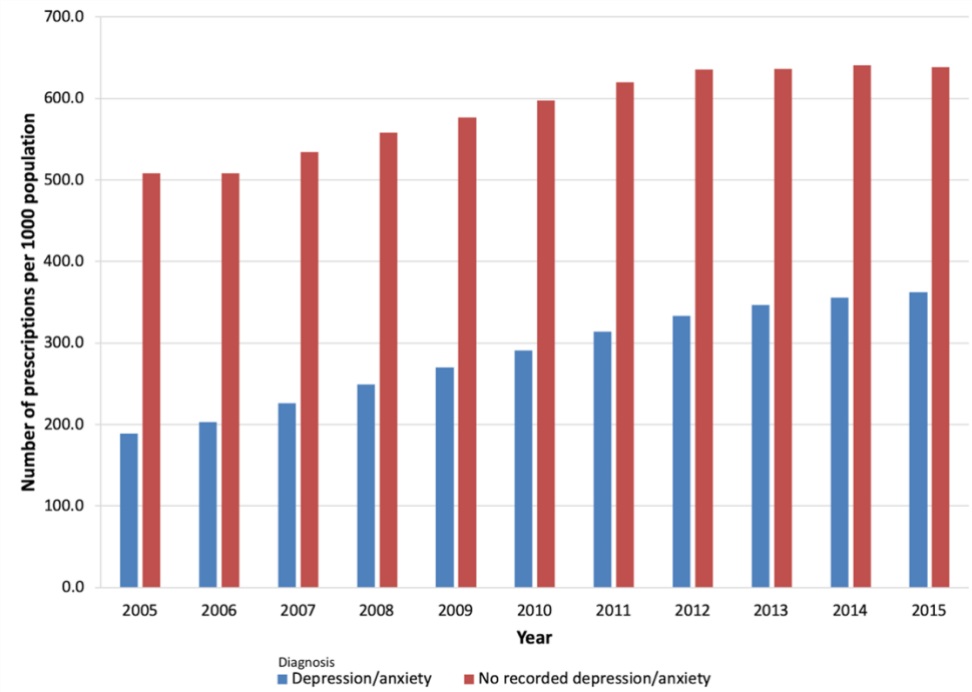


Figure H.4: Trends in the number of prescriptions per 1000 population with or without a recorded diagnosis of depression and/or anxiety

The annual number of prescriptions for strong opioids issued to people with an RDDA increased 474.3% (from 12.6 to 72.2 prescriptions per 1000 population) over the period examined, whereas the number for people without an RDDA increased 229.6% (from 27.6 to 90.9 prescriptions per 1000 population). There were 2.2 times fewer strong opioid prescriptions issued to people with a concurrent RDDA compared to those for people without such a diagnosis in 2005 (12.6 versus 27.6 prescriptions per 1000 population respectively). In 2015, the difference had reduced to 1.3 times (72.2 versus 90.9 prescriptions per 1000 population). The difference between the two groups; strong opioid prescriptions

for people with an RDDA (median=34.4 prescriptions per 1000 population) and those without (median=51.1 prescriptions per 1000 population), was not significant (U=37.0, p=.133, r=0.1).

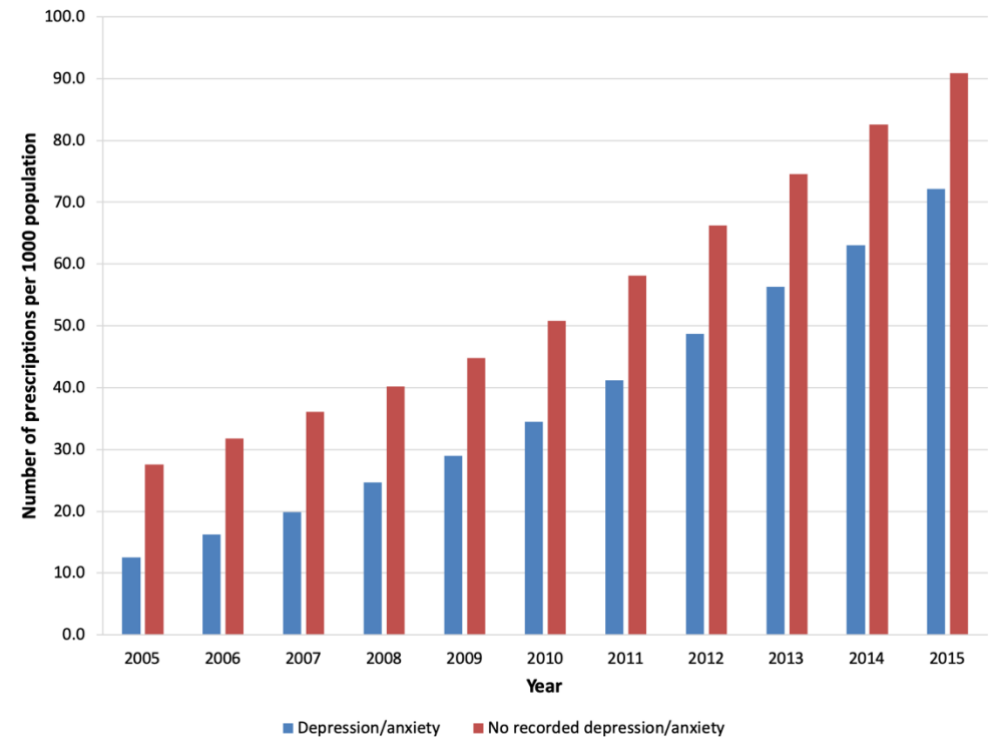


Figure H.5: Trends in the number of strong opioid prescriptions per 1000 population with or without a recorded diagnosis of depression and/or anxiety

Annual numbers of weak opioids being prescribed across the study period did not have such a high percentage increase as was seen with the strong opioid medicines. However, the annual number of weak opioid prescriptions for people with an RDDA increased 64.6% (from 176.3 to 290.1 prescriptions per 1000 people) and those without by 14.0% (from 480.4 to 547.5 prescriptions per 1000 people) in the same period.

The difference in the number of weak opioid prescriptions over the 11-year period examined for those with an RDDA (median=256.4 prescriptions per 1000 population) and the number issued to those without that diagnosis (median=546.6 prescriptions per 1000 population) was significant as determined by Mann-Whitney U test (U=<.001, p<.001, r=0.8).

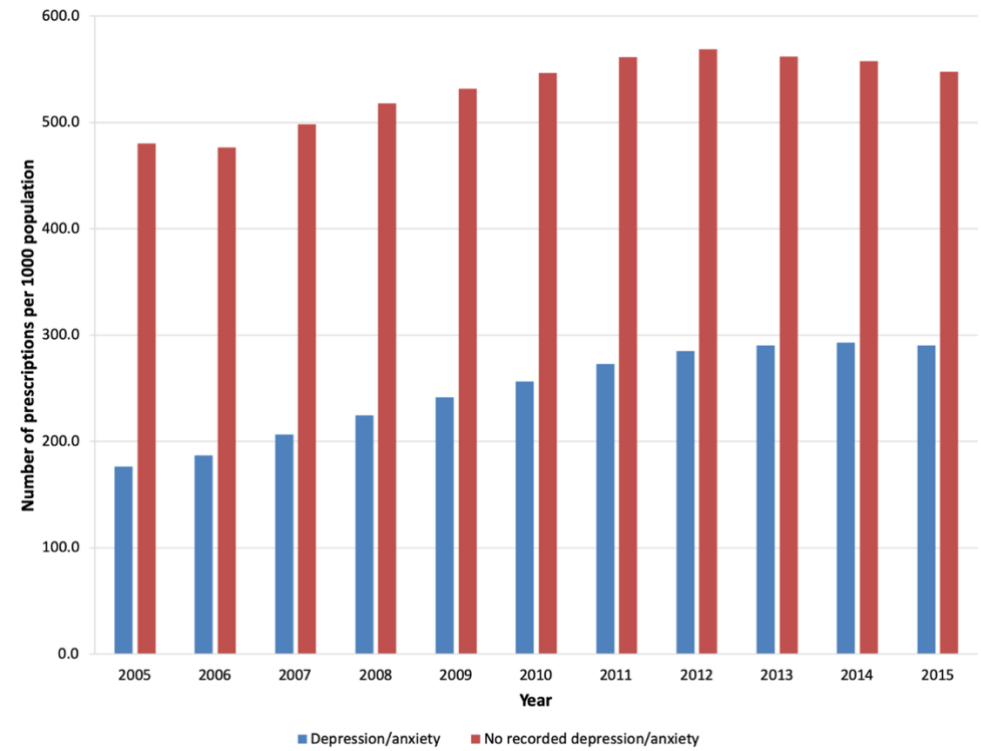


Figure H.6: Trends in the number of weak opioid prescriptions per 1000 population with or without a recorded diagnosis of depression and/or anxiety

Weak opioid prescriptions for people with an RDDA comprised 26.8% (176.3, n=656.6) of the total of weak opioids examined in 2005, rising to 34.6% (290.1, n=547.5) of the total in 2015. The difference between the number of prescriptions for people with an RDDA compared to those without changed from 2.7 times (176.3 versus 480.4 prescriptions per 1000 population) in 2005, to 1.8 times difference (290.1 versus 547.5 prescriptions per 1000 population) in 2015. There was a peak in the annual number of prescriptions for people without an RDDA in 2012. However, the peak in annual prescription numbers for people with an RDDA was seen in 2014.

H.2.3 Trends in the number of people receiving prescriptions by gender

Totalling annual data across the study period, twice as many women with a recorded diagnosis of depression and/or anxiety received prescriptions for opioids as men with the same recorded conditions (762,433 versus 350,391 respectively) in the 11 years examined. Over the 11 years examined, there was a median 28.7 men per 1000 male population who received prescriptions for opioid medicines and 59.4 women per 1000 female population who also had recorded diagnoses of depression and/or anxiety. Overall, 68% of the people with an RDDA and receiving opioid prescriptions were female. The difference between males and females with an RDDA and receiving opioid prescriptions was significant as determined by a Mann-Whitney U test (U=<.001, p<.001, r=0.8).

There were 3.3 times more men receiving opioid prescriptions who did not have an RDDA compared to those that did, averaged across the 11 years. Twice as

many women without an RDDA received opioid prescriptions than those with either of those diagnoses.

Table H.4: Sex differences in prescribing of weak and strong opioids in people with and without recorded diagnoses of depression/anxiety. Data adjusted to people per 1000 sex-adjusted population

Gender	People per 1000 population receiving opioid prescriptions					
	No recorded diagnosis of depression/anxiety			Recorded diagnosis of depression/anxiety		
	Weak opioid	Strong opioid	Total	Weak opioid	Strong opioid	Total
Male 2005	76.1	2.8	79.0	19.7	0.9	20.6
Male 2015	86.5	6.7	93.3	26.8	3.4	30.1
(% change rate)	13.7	136.5	18.1	36.1	277.1	46.6
Female 2005	103.1	3.7	106.7	43.4	1.4	44.9
Female 2015	104.0	9.7	113.7	56.7	6.6	63.3
(% change rate)	0.9	166.2	6.5	30.6	367.9	41.2

Over the 11 years examined, there was a 41.2% (from 44.9 to 63.3 women per 1000 female population) increase in the number of women with an RDDA receiving prescriptions for opioid medicines. Over the same time, the number of women without those diagnoses increased 6.5% (from 106.7 to 113.7 women per 1000 female population). There were peaks in the annual number of women receiving opioid prescriptions in 2012 for those without depression or anxiety and in 2014 for those with. As a consequence, the percentage of the total annual number of women receiving opioid prescriptions; the number who had an RDDA changed from 29.6% (44.9, n = 151.6 women per 1000 female population) in 2005 to 35.8% (63.3, n = 177 women per 1000 female population).

The number of men with an RDDA receiving opioid prescriptions between 2005 and 2015 rose 46.6% (from 20.6 to 30.1 men per 1000 male population) (Figure X). Men without an RDDA increased by 18.1% (from 79.0 to 93.3 men per 1000 male population) at the same time. Male data showed the same pattern of peak years as the female data already described although the percentage of the men receiving opioid prescriptions who had an RDDA changed from 20.7% (20.6, n = 99.6) in 2005 to 24.4% (30.1, n = 123.4 men per 1000 male population).

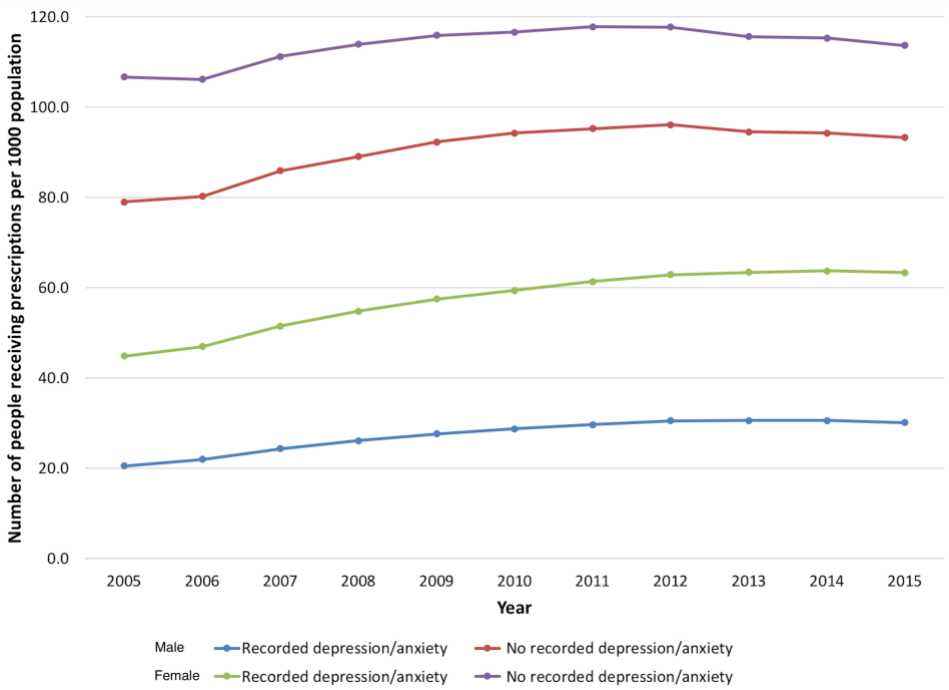


Figure H.7: Trends in opioid prescribing by sex and presence of a recorded diagnosis of depression/anxiety. Data presented by number of people per 1000 sex-adjusted population

The number of women with an RDDA receiving strong opioid prescriptions increased 367.9% (from 1.4 to 6.6 women per 1000 female population) in the 11 years analysed. Women without that recorded diagnosis increased in annual numbers by 166.2% (from 3.7 to .7 women per 1000 female population). There was a change in the difference between the two groups (RDDA versus none) of 2.6 times in 2005, reducing to 1.5 times difference in 2015. The difference between the two groups of women (median without an RDDA = 5.5 women per 1000 female population, median with an RDDA = 3.2 women per 1000 female population) receiving strong opioids was also determined significant although effect size was modest (U=20.0, p=.007, r=0.3).

There was a 277.1% (0.9 to 3.4 men per 1000 male population) increase in the number of men receiving strong opioid prescriptions during the study period. Men without an RDDA increased in annual numbers by 136.5% (from 2.8 to 6.7 men per 1000 male population). There were 3 times more men receiving prescriptions for strong opioids and whom did not have an RDDA than those that did, in 2005 and this fell to a 2 times difference in 2015. Mann-Whitney U tests demonstrated a significant difference (U=5.0, p<.001, r=0.6) between the number of men receiving strong opioids who did not have an RDDA (median=3.8 men per 1000 male population) and those with those diagnoses (median=1.7 men per 1000 male population) between 2005 and 2015.

Differences also existed between men and women receiving strong opioids with or without an RDDA. There were 1.6 times more women with an RDDA receiving strong opioid prescriptions than men in 2005 and this increased to 1.9 times difference in 2015. More women without an RDDA received strong opioid

prescriptions than men and this also increased over the study period, from 1.3 to 1.5 times difference (2005 to 2015 respectively).

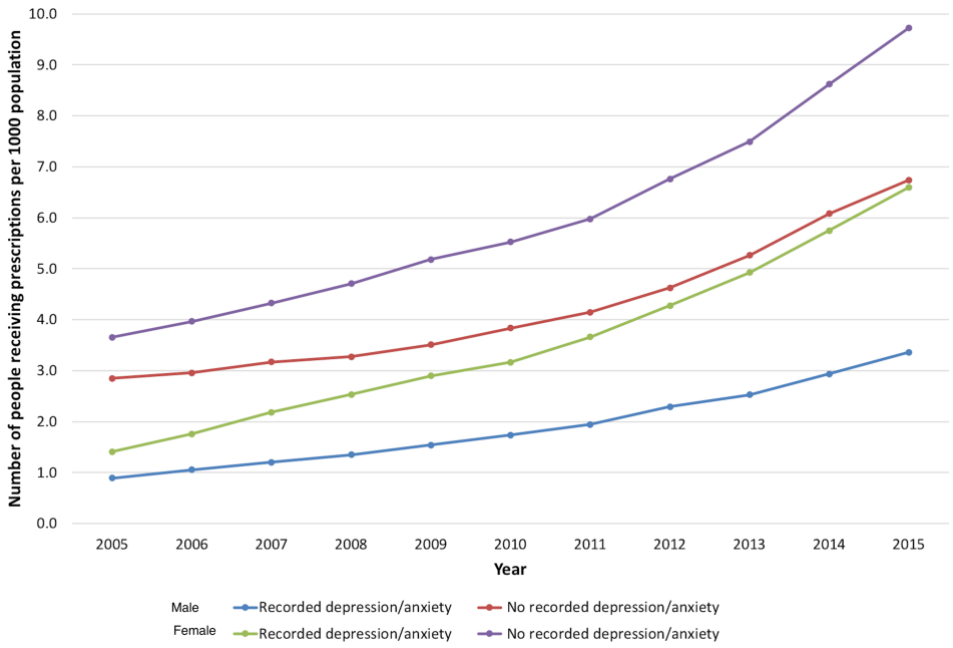


Figure H.8: Trends in strong opioid prescribing by sex and presence of a recorded diagnosis of depression/anxiety. Data presented by number of people per 1000 sex-adjusted population

As with strong opioids, the differences between women receiving weak opioids and who had an RDDA and those that did not, also reduced over the study period. The number of women with an RDDA receiving weak opioid prescriptions increased by 30.6% (from 43.4 to 56.7 women per 1000 female population). In contrast, women without an RDDA increased in number by 0.9% (from 103.1 to 104.0 women per 1000 female population) overall although there was a peak of 111.9 women per 1000 female population in 2011, which equated to an 8.6% increase from 2005. Although there was a greater percentage increase in the number of women with an RDDA receiving prescriptions, there were 1.8 times more women without an RDDA being issued with weak opioid prescriptions in 2015.

Using a Mann-Whitney U test, a significant difference (U=<.001, p<.001, r=0.8) between the number of women without an RDDA (median=108.1 women per 1000 female population) and women with that diagnosis (median=56.2 women per 1000 female population) was demonstrated.

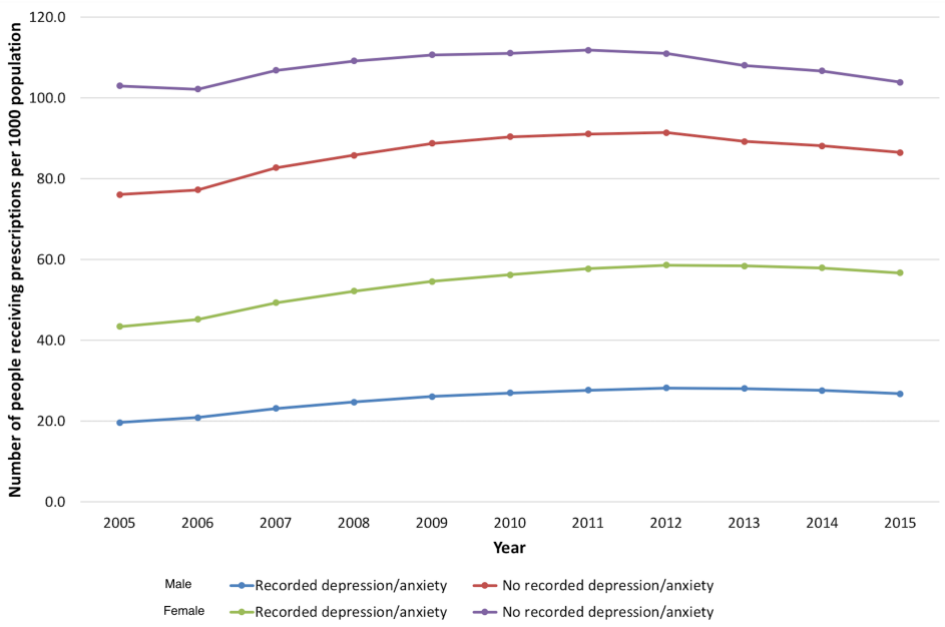


Figure H.9: Trends in weak opioid prescribing by sex and presence of a recorded diagnosis of depression/anxiety. Data presented by number of people per 1000 sex-adjusted population

Similarly, there was a greater percentage increase in the annual number of men with an RDDA receiving weak opioid prescriptions between 2005 and 2015, with a 36.1% (from 19.7 to 26.8 men per 1000 male population) in that time. Men without an RDDA being given weak opioid prescriptions however, rose in annual number by 13.7% (from 76.1 to 86.5 men per 1000 male population) but changed from being 3.9 times more men without an RDDA than those with in 2005, to being 3.2 times more in 2015.

The difference between the number of men without an RDDA (median=88.2 men per 1000 male population) and those with the diagnosis (median=26.8 men per 1000 male population), was statistically significant as derived by Mann-Whitney U test (U=<.001, p<.001, r=0.8).

H.2.4 Trends in the number of prescriptions by gender

As was seen with the number of people receiving prescriptions, there were twice as many opioid prescriptions issued to women with a recorded diagnosis of depression/anxiety as for men during the 11-year period examined (4,975,365 versus 2,490,992 respectively). The difference between the number of prescriptions issued to men (median=198.4 prescriptions per 1000 male population) and to women (median=379.8 prescriptions per 1000 female population) was statistically significant as determined by a Mann-Whitney U test (U=<.001, p<.001, r=0.8).

There were however, 1.8 times more prescriptions issued for women without an RDDA (9,017,570 actual prescriptions, median=689.1 prescriptions per 1000 female population). A Mann-Whitney U test demonstrated the difference between the numbers of prescriptions issued to the two groups of women was

significant (U=<.001, p<.001, r=0.8). Relatedly, 2.5 times more issued to men without an RDDA (6,302,638 prescriptions, median=502.2 prescriptions per 1000 male population) than those with those recorded diagnoses respectively. This was also determined statistically significant (U=<.001, p<.001, r=0.8).

Table H.5: Gender differences in prescription trends of weak and strong opioids with and without recorded diagnoses of depression/anxiety. Data adjusted to prescriptions per 1000 sex-adjusted population

	Prescriptions per 1000 population					
	No recorded diagnosis of depression/anxiety			Recorded diagnosis of depression/anxiety		
Gender	Weak opioid	Strong opioid	Total	Weak opioid	Strong opioid	Total
Male 2005	383.3	25.1	408.4	113.1	11.6	124.6
Male 2015	474.0	77.3	551.3	191.7	52.7	244.4
(% change rate)	23.6	208.3	35.0	69.5	356.0	96.0
Female 2005	572.7	30.0	602.7	236.4	13.5	249.9
Female 2015	618.9	104.2	723.0	385.5	91.1	476.5
(% change rate)	8.1	247.5	20.0	63.1	573.0	90.7

When adjusted to the relevant population, there was a 90.7% (from 249.9 to 476.5 prescriptions per 1000 population) increase in the number of prescriptions for women with an RDDA over the period examined. There were 2.4 times more prescriptions issued to women without an RDDA in 2005 and over the following 11 years, the annual number of prescriptions issued to that group increased by 20% (from 602.7 to 723.0 prescriptions per 1000 female population), reducing the difference to 1.5 times between the non-RDDA and RDDA groups respectively. These changes in the number of prescriptions issued resulted in prescriptions for women with an RDDA accounting for 29.3% of the total of prescriptions issued in 2005, increasing to 39.7% of the total in 2015.

The annual number of prescriptions for men with an RDDA rose 96.0% (from 124.6 to 244.4 prescriptions per 1000 male population) whilst, for men without those diagnoses, annual prescription numbers grew 35.0% (from 408.4 to 551.3 prescriptions per 1000 male population). As a consequence of the changes in prescribing trends prescriptions for men without an RDDA changed from being 3.3 times greater in number in 2005 than for men with an RDDA, to 2.3 times greater in 2015. In terms of percentage of the total number of prescriptions being issued over those years, in 2005 opioid prescriptions for men with an RDDA comprised 23.4% and rose to 30.7% of the total in 2015. Unlike with other trends already reported, there was no peak in the annual number of prescriptions issued to people of either sex who had a concurrent RDDA. The data demonstrated that the annual number of prescriptions for those groups of people increased every year between 2005 and 2015, although the rate of change appeared to slow in the last 3 years of the study period (**Error! Reference source not found.**).

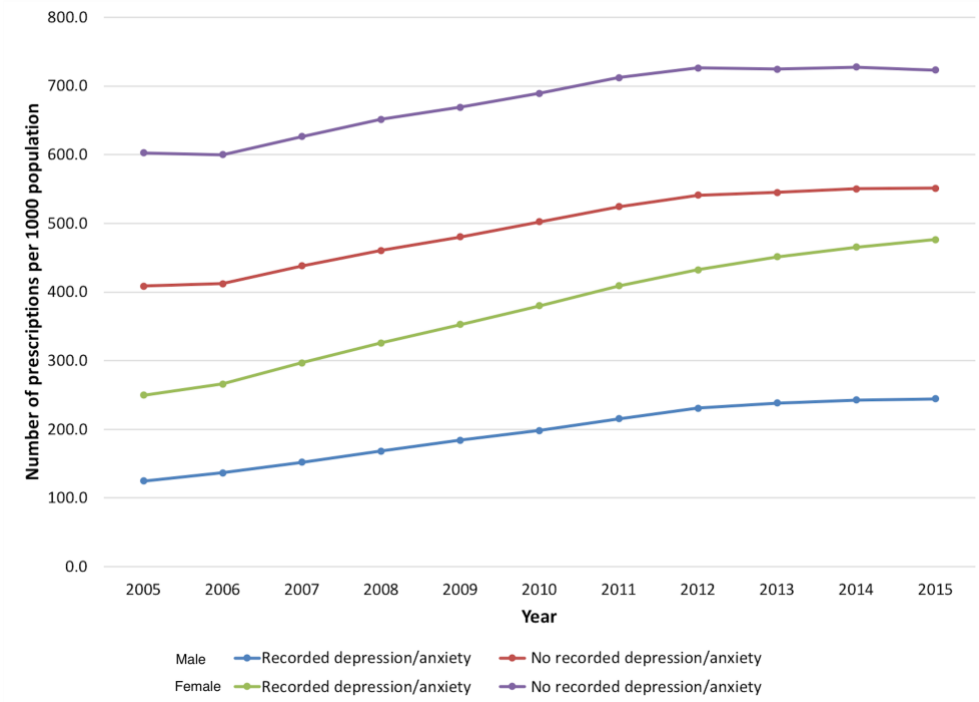


Figure H.10: Trends in the number opioid prescribing by gender and presence of a recorded diagnosis of depression/anxiety. Data presented by number of people per 1000 sex-adjusted population

Strong opioid prescriptions for women with an RDDA rose 573% (from 13.5 to 91.1 prescriptions per 1000 female population, median=42.0 prescriptions per 1000 female population) between 2005 and 2015. At the same time, the annual number of prescriptions for women without an RDDA increased 247.5% (from 30.0 to 104.2 prescriptions per 1000 female population, median=59.0 prescriptions per 1000 female population). Based on Mann-Whitney U tests, there was no significant difference between the number of strong opioid prescriptions being issued to women with or without an RDDA (U=37.0, p=.133, r=0.1).

Strong opioid prescriptions for women with an RDDA changed from accounting for 31.1% of the annual total being issued to women in 2005, to 46.6% of the total in 2015. The faster rate of change in the annual number of prescriptions issued to women with an RDDA also resulted in a narrowing of the difference between that group and women without those diagnoses. Consequently, in 2005 there were 2.2 times more prescriptions issued to women without an RDDA compared to those with and this changed to a 1.14 times difference in 2015.

Men with an RDDA had a 356% (from 11.6 to 52.7 prescriptions per 1000 population, median=42.5 prescriptions per 1000 male population) increase in the number of strong opioid prescriptions issued over the study period. Men without an RDDA had a 208.3% (from 25.1 to 77.3 prescriptions per 1000 population, median=26.6 prescriptions per 1000 population) increase in the annual number of prescriptions issued. Differently to women, there was a statistically significant difference between the number of strong opioid prescriptions being issued to men with and without an RDDA (U=5.0, p<.001, r=0.6).

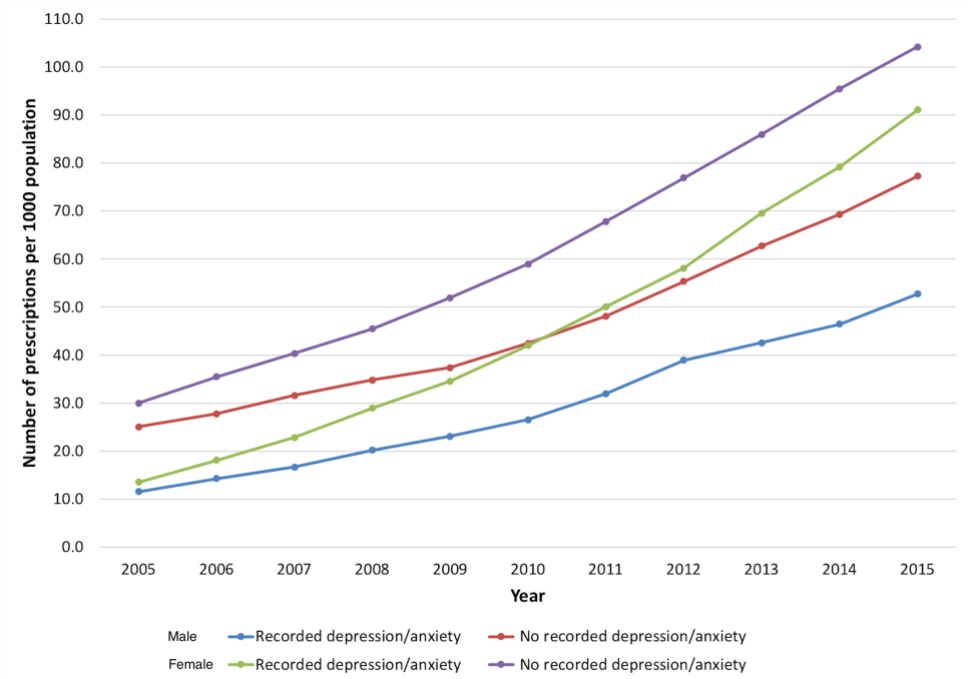


Figure H.11: Trends in the number of strong opioid prescriptions by sex and presence of a recorded diagnosis of depression/anxiety. Data presented by number of prescriptions per 1000 sex-adjusted population

Proportionally, the annual number of prescriptions for men with an RDDA was 31.6% (11.6, n = 36.7) of the total number issued in 2005 and increased to 40.6% (52.7, n = 130) of the total number of prescriptions issued in 2015. As was seen in the female group, there was a narrowing of the difference between the two groups of men whose prescriptions were examined. There were 2.2 times more prescriptions issued to men without an RDDA in 2005 than men with the diagnoses. This changed to a 1.5 times difference in the number of prescriptions issued in 2015.

Annual number of weak opioid prescriptions for women with an RDDA increased 63.1% (from 236.4 to 385.5 prescriptions per 1000 female population, median=337.8 prescriptions per 1000 female) compared to an 8.1% increase (from 572.7 to 618.9 prescriptions per 1000 female population, median=618.9 prescriptions per 1000 female population) for women without those diagnoses (Figure X). Mann-Whitney U tests determined the difference between the number of prescriptions issued to each group was significant (U=<.001, p<.001, r=0.8).

The percentage of weak opioid prescriptions issued to women with an RDDA changed from 29.2% to 38.4% of the total of weak opioid prescriptions issued to women between 2005 and 2015. Further, in 2005 there were 2.4 times more weak opioid prescriptions issued to women without an RDDA than those with, which reduced to a 1.6 times difference between the groups in 2015 (Table X).

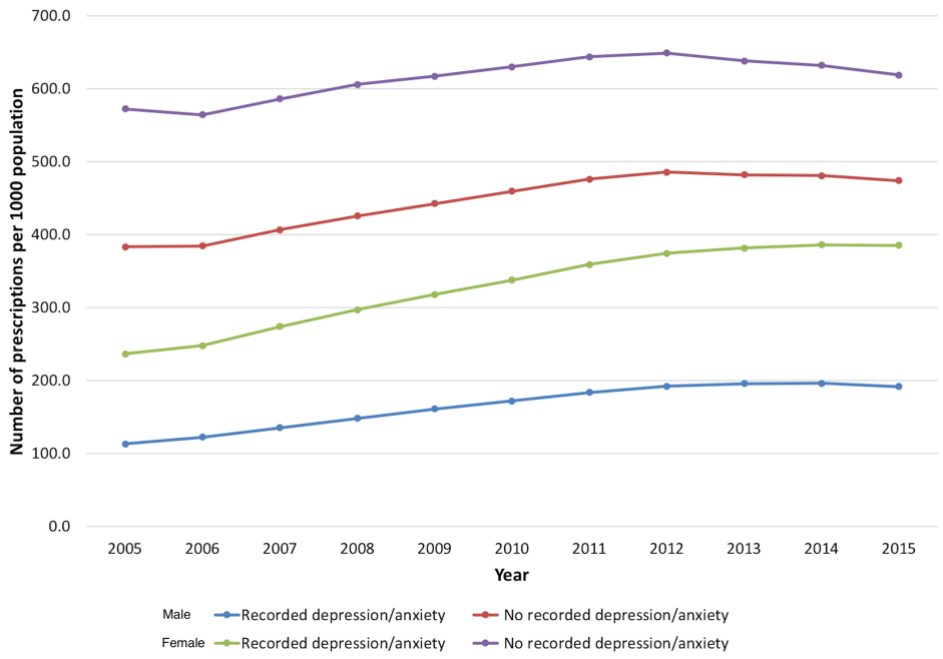


Figure H.12: Trends in the number of weak opioid prescribing by gender and presence of a recorded diagnosis of depression/anxiety. Data presented by number of prescriptions per 1000 gender-adjusted population

There were 3.4 times more weak opioid prescriptions issued to men without an RDDA in 2005 which changed to 2.5 times more in 2015. This corresponded with a 69.5% (from 113.1 to 191.7 prescriptions per 1000 male population, median=171.8 prescriptions per 1000 male population) increase in the annual number of weak opioid prescriptions issued to men with an RDDA compared to 23.6% (from 383.3 to 474.0 prescriptions per 1000 population, median=459.7 prescriptions per 1000 male population) in the men without those diagnoses. The difference in the number of prescriptions issued to each group was determined significant (U=<.001, p<.001, r=0.8).

The percentage of the total weak opioid prescriptions, that were issued to men with an RDDA rose from 22.8% of the total in 2005 to 28.8% of the total issued in 2015. Unlike the annual number of prescriptions issued to women with an RDDA, which increased every year of the period examined, those for men with that diagnosis peaked in 2014.

Appendix I Results stratified by Health Board

I.1 Health Board level data

Since 1 October 2009, NHS health care has been delivered via 7 Integrated Local Health Boards in Wales (NHS Wales 2009). In April 2019, Abertawe Bro Morgannwg University Health Board and Cwm Taf University Board, had their borders and consequently, populations altered. The newly formed Swansea Bay University Health Board no longer contains the Bridgend locality which, transferred to newly named Cwm Taf Morgannwg University Health Board. Consequently, data since April 2019 reflects these changes and would need to be considered for future research.

Within each Health Board exist smaller geographic units known as Lower Super Output Areas (LSOA). The LSOA generally have around 1500 population and are used to assign their respective Welsh Index of Multiple Deprivation (WIMD) score. They were devised from areas used in the 2001 Census (StatsWales 2010). SAIL datasets were formulated using LSOA level data and linked to the appropriate Health Board. Whilst it is possible to examine data to an individual practice level; beyond deprivation and general geographic area (Health Board) it was decided not to explore the data to that level at this stage.

I.2 Opioid prescribing by Health Board

I.2.1 Total opioid prescribing

Population adjusted data identified differences in the numbers of people receiving opioid prescriptions between 2005 and 2015 in the seven different Health Boards providing primary care services in Wales (Figure I.1).

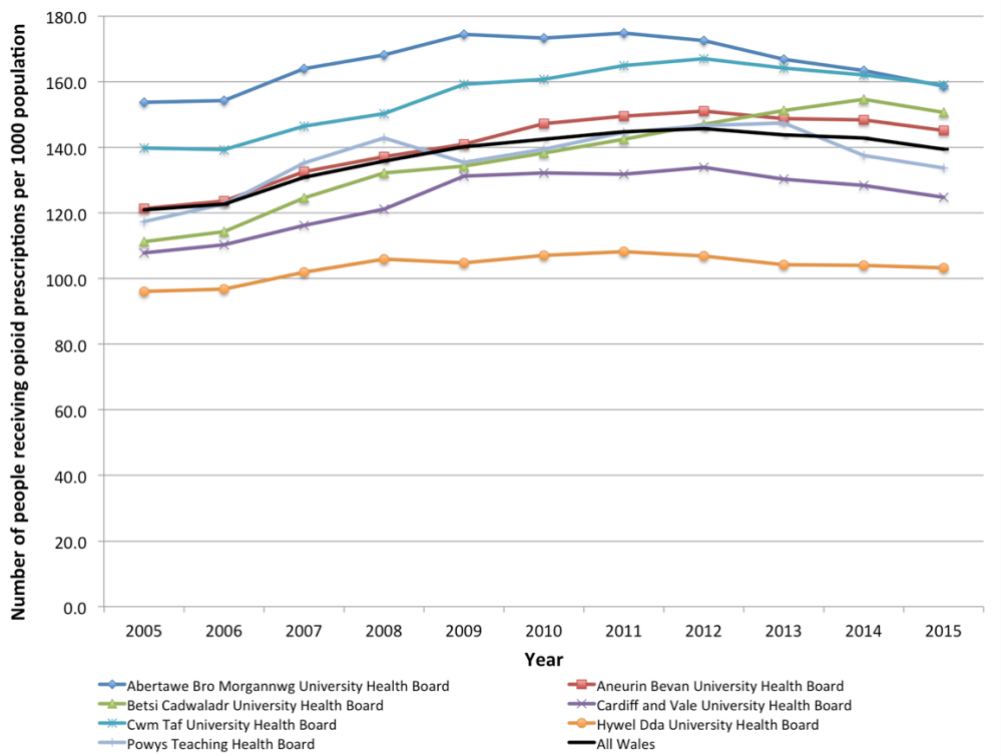


Figure I.1: Trend in the annual number of people per 1000 population receiving opioid prescriptions in each Health Board in Wales and compared to the National average. Data population adjusted to each Health Board

Abertawe Bro Morgannwg University Health Board (ABMUHB), Aneurin Bevan University Health Board (ABUHB) and Cwm Taf University Health Board (CTUHB) all had numbers of people receiving opioid prescriptions consistently above the National average for Wales (Table I.2) for the 11-year study period.

A Kruskal-Wallis test provided very strong evidence of a difference ($p<.001$) between the mean ranks of the pairs of groups of the different Health Boards when examining the difference in the number of people receiving opioid prescriptions. Dunn's pairwise tests were carried out for the 21 pairs of groups and showed that 9 pairs of Health Board comparisons were significantly different for the number of people prescribed opioids. The remaining 12 pairs were not significantly different (Table I.1).

Table I.1: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of people receiving opioid prescriptions by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	.084					
BCUHB	.021	>.999				
CVUHB	<.001*	.830	>.999			
CTUHB	>.999	>.999	.541	.002*		
HDUHB	<.001*	.004*	.018*	>.999	<.001*	
PTHB	.013*	>.999	>.999	>.999	.371	.030*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health

Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Population adjusted data demonstrated that whilst Powys has the smallest population in Wales, in terms of numbers; the number of people receiving opioid prescriptions per 1000 population were similar to some of the more densely populated Health Boards (Table I.2).

I.2.2 Number of prescriptions issued

Annual prescription numbers per 1000 population rose in every Health Board between 2005 and 2011 (Figure I.2). Betsi Cadwaladr University Health Board (BCUHB) had the largest increase in annual prescription numbers in Wales, with a 78.1% (from 527.9 to 940.5 prescriptions per 1000 population) rise over the 11 years of the study.

Table I.2: Trends in the annual number of people receiving opioid prescriptions in each Health Board in Wales and compared to the National Average (All Wales). Percentage change over the 11 year study period included. Data population adjusted per Health Board (number of people per 1000 population)

	Health Board*															
	ABMUHB		ABUHB		BCUHB		CVUHB		CTUHB		HDUHB		PTHB		All Wales	
Number of people - change rate(%)																
2005	153.7		121.3		111.2		107.8		139.8		96.1		117.4		120.9	
2006	154.3	0.4	123.5	1.9	114.3	2.8	110.3	2.3	139.3	-0.3	96.8	0.7	122.7	4.5	122.7	1.5
2007	164.0	6.3	132.6	7.3	124.6	9.0	116.3	5.4	146.5	5.2	101.9	5.3	135.3	10.	130.9	6.7
2008	168.2	2.6	137.1	3.4	132.1	6.1	121.1	4.2	150.3	2.6	105.9	3.9	142.8	3	135.9	3.8
2009	174.5	3.7	141.0	2.8	134.2	1.6	131.1	8.3	159.3	6.0	104.7	-1.2	135.3	5.5	140.2	3.2
2010	173.3	-0.7	147.1	4.4	138.2	3.0	132.2	0.8	160.7	0.9	107.0	2.2	139.4	-5.2	142.5	1.6
2011	174.8	0.8	149.5	1.6	142.4	3.1	131.9	-0.2	164.9	2.6	108.2	1.1	144.5	3.0	144.7	1.5
2012	172.6	-1.3	151.0	1.0	147.0	3.2	133.8	1.5	166.9	1.2	106.9	-1.2	146.7	3.7	145.7	0.7
2013	166.9	-3.3	148.7	-1.5	151.3	2.9	130.3	-2.6	164.2	-1.6	104.3	-2.4	147.4	1.5	143.8	-1.3
2014	163.3	-2.1	148.3	-0.3	154.7	2.2	128.5	-1.4	162.0	-1.4	103.9	-0.3	137.6	0.5	142.9	-0.7
2015	158.7	-2.8	145.2	-2.1	150.7	-2.6	124.7	-2.9	159.0	-1.8	103.3	-0.7	133.7	-6.7	139.5	-2.4
														-2.8		
Median	166.9		145.2		138.2		128.5		159.3		104.3		137.6		140.2	
Percentage change 2005-2015 (%)	3.2		19.7		35.5		15.7		13.8		7.5		13.9		15.4	

*ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

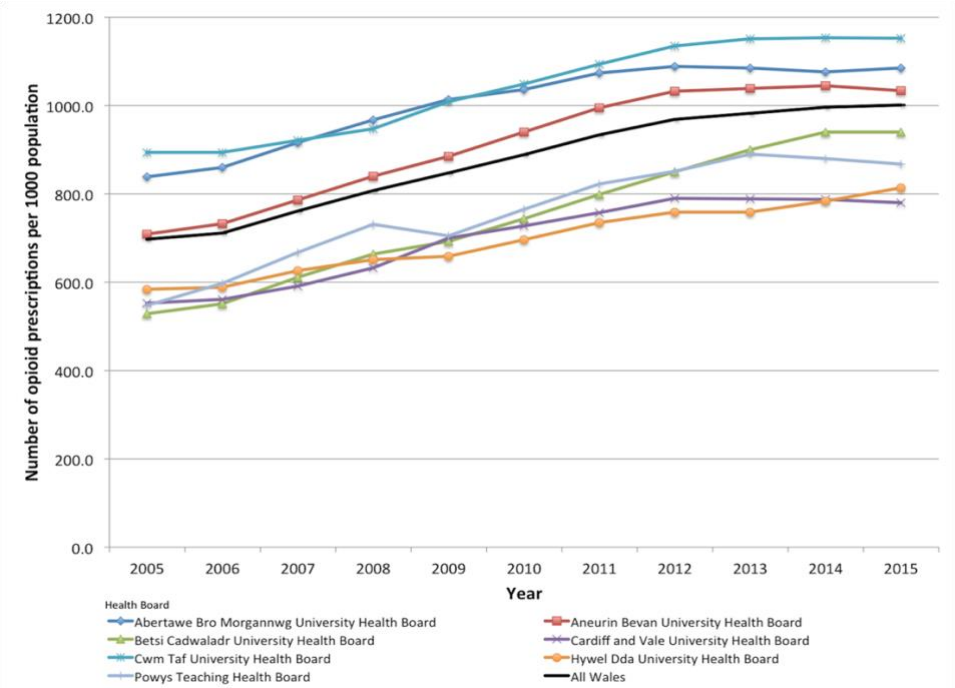


Figure I.2: Trend in the annual number of prescriptions per 1000 population in each Health Board in Wales and compared to the National trend. Data population adjusted to each Health Board

Kruskal-Wallis test demonstrated a strong difference (p<.001) between the number of opioid prescriptions issued between Health Boards across Wales over the 11 years examined. Dunn's pairwise comparisons and post-hoc Bonferroni tests highlighted significant difference between 8 pairs of comparisons of the number of prescriptions issued in the Health Boards.

Table I.3: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of opioid prescriptions being issued by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	>.999					
BCUHB	.014*	.672				
CVUHB	.001*	.080	>.999			
CTUHB	>.999	>.999	.003*	<.001*		
HDUHB	<.001*	.055	>.999	>.999	<.001*	
PTHB	.019*	.840	>.999	>.999	.004*	>.999

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

In 2005, CTUHB, the organisation with the highest number of annual prescriptions, had 1.7 times more prescriptions issued per 1000 population than BCUHB, which had the fewest number. However, due to the large increase in annual numbers of prescriptions in BCUHB, by 2015 it was the fourth highest prescriber. Cardiff and Vale University Health Board (CVUHB), despite having a 41.1% increase in annual prescription numbers over the study period was by

2015, the Health Board with the fewest opioid prescriptions per 1000 population (Table I.4).

Table I.4: Trends in the annual number of opioid prescriptions in each Health Board in Wales and compared to the National Average (All Wales). Rate change over the 11 year study period included. Data population adjusted per Health Board (number of people per 1000 population)

	Health Board															
	ABMUHB		**ABUHB**		**BCUHB**		**CVUHB**		**CTUHB**		**HDUHB**		**PTHB**		**All Wales**	
Number of people – change rate (%)																
2005	838.2		708.7		527.9		552.5		893.9		583.9		547.2		696.8	
2006	859.5	2.5	732.8	3.4	551.1	4.4	560.7	1.5	894.2	0.0	588.8	0.9	597.2	9.1	711.4	2.1
2007	916.2	6.6	786.6	7.3	610.6	10.8	590.6	5.3	921.6	3.1	625.8	6.3	667.4	11.8	760.6	6.9
2008	967.0	5.6	840.1	6.8	663.5	8.7	632.8	7.2	947.2	2.8	651.4	4.1	730.5	9.5	807.1	6.1
2009	1013.4	4.8	884.5	5.3	691.9	4.3	700.3	10.7	1009.1	6.5	658.6	1.1	705.4	-3.4	846.8	4.9
2010	1035.9	2.2	940.5	6.3	743.3	7.4	727.5	3.9	1049.1	4.0	696.5	5.8	765.0	8.4	888.2	4.9
2011	1073.4	3.6	994.4	5.7	798.9	7.5	757.1	4.1	1093.9	4.3	734.2	5.4	821.7	7.4	933.8	5.1
2012	1089.0	1.5	1031.9	3.8	849.4	6.3	789.5	4.3	1134.4	3.7	759.0	3.4	851.5	3.6	968.7	3.7
2013	1084.7	-0.4	1038.3	0.6	899.3	5.9	789.0	-0.1	1150.6	1.4	758.8	0.0	890.0	4.5	982.8	1.5
2014	1076.5	-0.8	1045.3	0.7	939.6	4.5	787.6	-0.2	1153.5	0.3	784.1	3.3	879.6	-1.2	996.2	1.4
2015	1085.3	0.8	1033.1	-1.2	940.5	0.1	779.6	-1.0	1152.4	-0.1	813.9	3.8	867.6	-1.4	1000.7	0.5
Median	1035.9		940.5		743.3		727.5		1049.1		696.5		765.0		888.2	
Rate change 2005-2015 (%)	29.5		45.8		78.1		41.1		28.9		39.4		58.6		43.6	

*ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

I.2.3 Types of opioids being prescribed

The trend in the numbers of prescriptions being issued in each Health Board across Wales varied depending on the type of opioid (weak or strong) being prescribed (Table I.5).

Table I.5: Trends in the number of opioid prescriptions per 1000 population, issued in each Health Board. Adjusted to annual Health Board population

Number of prescriptions	Health Board*						
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB
Strong opioids							
2005	35.0	34.3	40.1	33.5	46.3	47.9	28.5
2015	160.7	158.9	158.9	143.2	138.3	169.8	145.3
Median	61.5	82.4	94.1	86.7	82.0	91.9	64.3
Change rate (%)	359.5	363.7	296.0	326.9	198.4	254.1	410.4
Weak opioids							
2005	803.3	674.5	487.8	519.0	847.5	535.9	518.7
2015	924.6	874.2	781.5	636.4	1014.2	644.2	722.3
Median	948.6	858.1	653.2	636.4	967.1	604.6	700.7
Change rate (%)	15.1	29.6	60.2	22.6	19.7	20.2	39.2

*ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Large increases in the number of strong opioid prescriptions being issued were observed in each Health Board (Figure I.3), the greatest seen in Powys Teaching Health Board (410.4%, from 28.5 to 145.3 prescriptions per 1000 population). The lowest percentage increase in the annual number of strong opioid prescriptions was seen in Cwm Taff University Health Board although the annual number of prescriptions nearly tripled over the 11 years examined.
A Kruskal-Wallis test of the differences in the annual numbers of strong prescriptions between each Health Board did not demonstrate significance (p=.695). As a result, Dunn's pairwise tests and post-hoc Bonferroni tests were not undertaken.

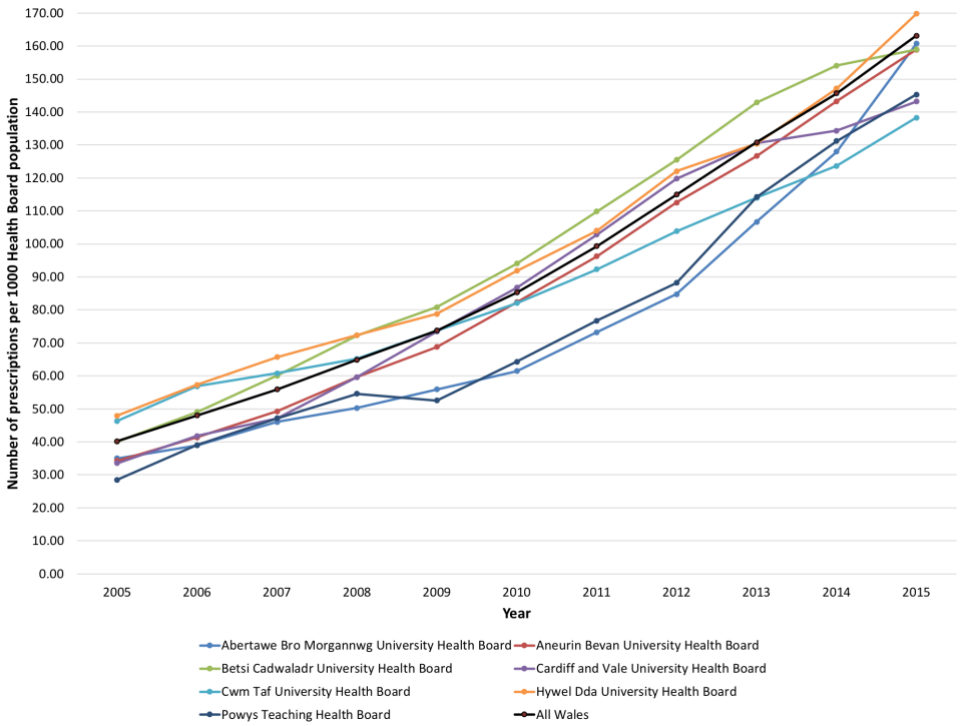


Figure I.3: Trend in the annual number of strong opioid prescriptions in each Health Board and compared to the National trend. Data population adjusted to Health Board

Trends in the annual number of weak opioid prescriptions being issued within each of the seven Health Boards showed more variation than was seen with strong opioid prescriptions (Figure I.3).

Abertawe Bro Morgannwg University Health Board demonstrated the smallest increase in annual prescription numbers (15.1%, from 803.3 to 924.6 prescriptions per 1000 population) although had the second highest rate of prescribing in Wales. Again, as with the strong opioid prescriptions, Powys Teaching Health Board had the greatest percentage increase in annual prescription numbers from 2005 to 2015 (39.2%, from 518.7 to 722.3 prescriptions per 1000 population).

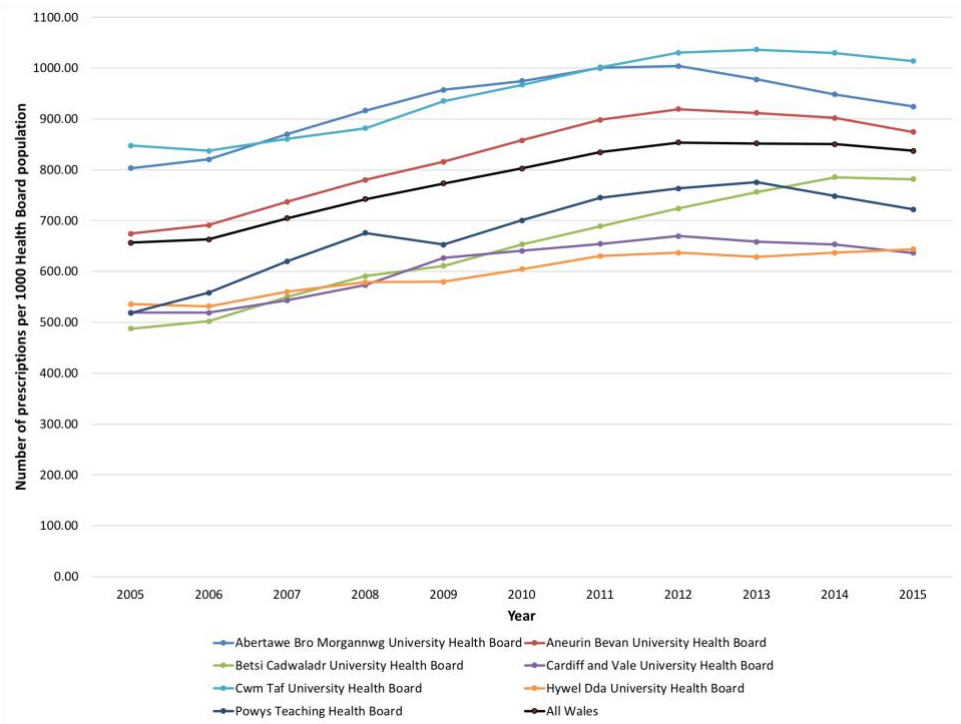


Figure I.4: Trend in the annual number of weak opioid prescriptions in each Health Board and compared to the National trend. Data population adjusted to Health Board

A significant difference was demonstrated between the number of weak opioid prescriptions being issued in each Health Board, as determined by Kruskal-Wallis test (p<.001). Dunn's pairwise and post-hoc Bonferroni tests showed significant differences between 10 pairs of Health Board data (Table I.6). The 11 other pairs were not statistically different.

Table I.6: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of weak opioid prescriptions being issued by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	>.999					
BCUHB	.002*	.184				
CVUHB	<.001*	.023*	>.999			
CTUHB	>.999	>.999	.001*	<.001*		
HDUHB	<.001*	.007*	>.999	>.999	<.001*	
PTHB	.013*	.757	>.999	>.999	.005*	>.999

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

I.3 Opioid prescribing by deprivation per Health Board

There was variance between the seven Health Boards in Wales, in respect of opioid prescribing in the different areas of deprivation (Table I.9).

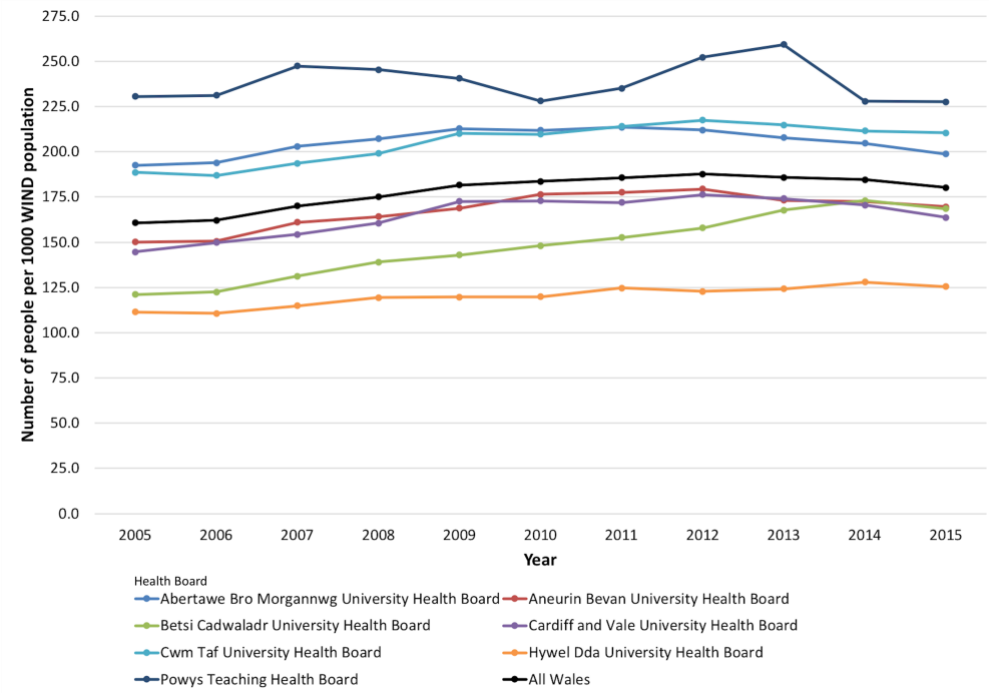


Figure I.5: Trend in the number of people receiving prescriptions for opioid medicines in the most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD1 areas in each Health Board

Powys Teaching Health Board (PTHB), whilst having the smallest population of all the Health Boards in Wales, had the greatest number of people in the most deprived areas, receiving opioid prescriptions over the whole 11 period examined, despite a small reduction in numbers within the Health Board itself (-1.3%, from 230.5 to 227.6 people per 1000 WIMD1 population) (Table I.4).

The greatest increase in number of people in WIMD1 areas (39.2%, from 121.1 to 168.5 people per 1000 WIMD1 population) receiving opioid prescriptions was in Betsi Cadwaladr University Health Board (BCUHB).

A Kruskal-Wallis test demonstrated a significant difference (p<.001) between the number of people receiving opioid prescriptions in WIMD1 areas in the 7 Health Boards. Post-hoc analysis demonstrated significant difference (p<.05) between 8 of the 21 pairs of comparators WIMD1 areas within the Health Board areas, the remaining pairs did not have a statistical difference between them.

Table I.7: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of people receiving opioid prescriptions being issued in WIMD1 areas (most deprived) by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	.411					
BCUHB	.005*	>.999				
CVUHB	.189	>.999	>.999			
CTUHB	>.999	.325	.004*	.147		
HDUHB	<.001*	.139	>.999	.309	<.001*	
PTHB	>.999	.001*	<.001*	>.999	.005*	<.001*

*p <0.05 = statistically significant **ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

The highest numbers of people per 1000 population in WIMD2 areas receiving opioids, was again highest in PTHB (Table I.9), the area with the smallest population. Whilst there was variation over the 11 years examined (Figure I.6), there was overall a 17.1% (from 288.7 to 338.2 people per 1000 population) increase in the numbers between 2005 and 2015.

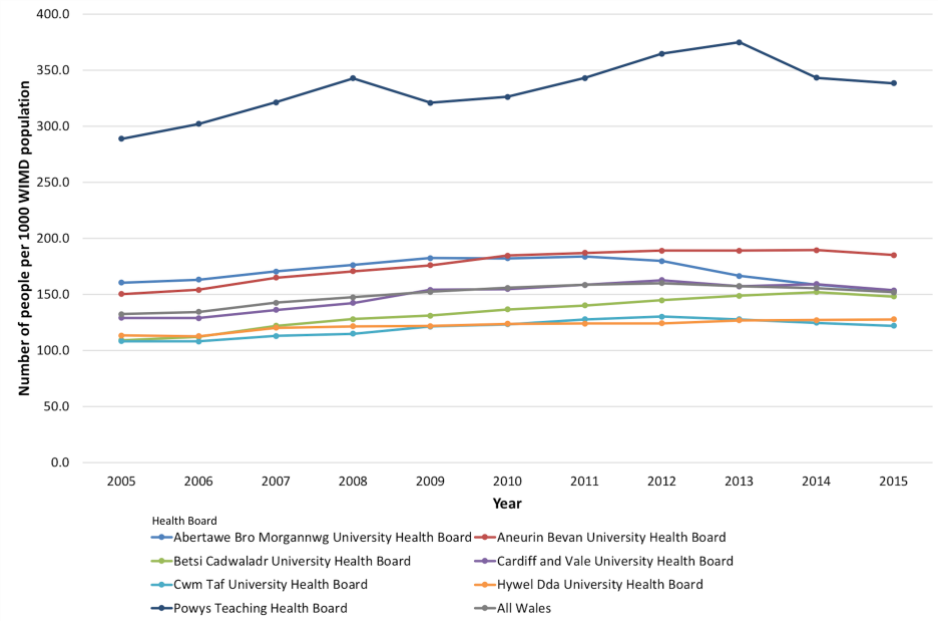


Figure I.6: Trend in the number of people receiving prescriptions for opioid medicines in the 2nd most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD2 areas in each Health Board

The greatest increase in the annual number of people receiving opioid prescriptions in WIMD2 areas was in BCUHB although 4 other Health Boards had larger levels of prescribing overall. The difference between the numbers of people living in WIMD2 areas and receiving opioid prescriptions was statistically significant as evaluated by Kruskal-Wallis tests (p<.001). Dunn's pairwise tests and post-hoc Bonferroni tests showed that 9 out of 21 pairs of WIMD2 areas in different Health Boards had significant differences in the numbers of people receiving prescriptions (Table I.8).

Table I.8: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of people receiving opioid prescriptions being issued in WIMD2 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	>.999					
BCUHB	.099	.026*				
CVUHB	>.999	>.999	>.999			
CTUHB	.001*	<.001*	>.999	.165		
HDUHB	.002*	<.001*	>.999	.239	>.999	

PTHB	.850	>.999	<.001*	.010*	<.001*	<.001*

*p <0.05 = statistically significant **ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Cwm Taff University Health Board had overall the largest number of people per 1000 population in WIMD3 areas of any of the seven Health Boards and was subject to a 15.2% (from 157.3 to 181.2 people per 1000 population) between 2005 and 2015 (Table I.9).

Hywel Dda University Health Board had the least number of people receiving prescriptions in WIMD3 areas over the same period. Although the smallest increase in numbers appeared to be in PTHB (2.2%, from 156.4 to 159.8 people per 1000 population), there was some fluctuation in the data from that Health Board over the study period.

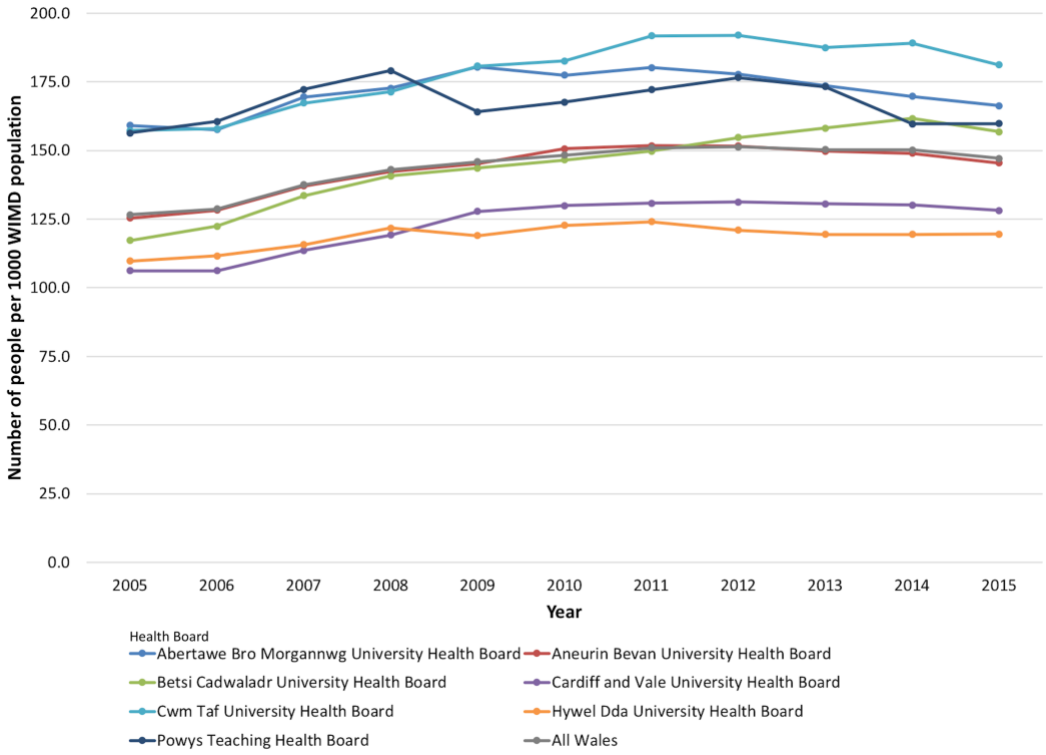


Figure I.7: Trend in the number of people receiving prescriptions for opioid medicines in the WIMD3 areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD3 areas in each Health Board

Table I.9: Trends in the annual number of people receiving opioid prescriptions in each Health Board in Wales by Welsh Index of Multiple Deprivation (WIMD) area

	Health Board						
Number of people per 1000	**ABMUHB**	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**	**PTHB**
All opioids							
WIMD1							
2005	192.5	150.0	121.1	144.7	188.6	111.4	230.5
2015	198.8	169.6	168.5	163.6	210.4	125.4	227.6
Median	207.1	169.6	148.0	170.6	210.2	119.9	235.1
Rate change 2005-2015 (%)	3.3	13.1	39.2	13.1	11.6	12.6	-1.3
WIMD2							
2005	160.5	150.2	109.1	129.0	108.2	113.2	288.7
2015	153.0	185.0	147.9	153.6	121.8	127.8	338.2
Median	170.4	184.4	136.4	154.0	121.8	123.7	338.2
Rate change 2005-2015 (%)	-4.7	23.2	35.6	19.1	12.6	12.9	17.1
WIMD3							
2005	159.1	125.4	117.3	106.3	157.3	109.7	156.4
2015	166.3	145.5	156.8	128.2	181.2	119.6	159.8
Median	172.7	145.5	146.6	128.2	181.2	119.5	167.6
Rate change 2005-2015 (%)	4.5	16.0	33.7	20.6	15.2	9.0	2.2
WIMD4							
2005	154.0	89.1	76.7	95.3	116.4	99.0	69.1
2015	167.1	115.5	104.6	114.0	130.6	101.3	83.3
Median	172.1	115.5	96.8	115.7	134.2	106.3	88.1
Rate change 2005-2015 (%)	8.4	29.6	36.3	19.6	12.2	2.3	20.5
WIMD5							
2005	101.9	71.7	112.2	84.9	103.3	31.5	75.8
2015	111.2	92.1	147.0	95.9	130.1	28.2	106.7
Median	114.0	87.8	140.3	98.5	131.7	33.0	109.8
Rate change 2005-2015 (%)	9.1	28.4	31.0	13.0	25.9	-10.5	40.8

*ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board. WIMD1=most deprived and WIMD5=least deprived area. Rate change over the 11-year study period included. Data population adjusted per Health Board (number of people per 1000 population)

A Kruskal-Wallis test demonstrated significance in the numbers of people receiving opioid prescriptions in the WIMD3 areas in each Health Board, although post-hoc testing demonstrated that this significance was between 8 of the 21 pairs of Health Board comparators (Table I.10).

Table I.10: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of people receiving opioid prescriptions being issued in WIMD3 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	.067					
BCUHB	.096	>.999				
CVUHB	<.001*	>.999	>.999			
CTUHB	>.999	.008*	.013*	<.001*		
HDUHB	<.001*	.508	>.999	>.999	<.001*	
PTHB	>.999	.227	.313	.001*	>.999	.375

*p <0.05 = statistically significant **ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

In the areas of Wales designated WIMD4, areas of lesser overall deprivation, Abertawe Bro Morgannwg University Health Board (ABMUHB) had the highest number of people receiving opioid prescriptions (Table I.9). Five of the remaining 6 Health Boards had significant differences in the number of people receiving prescriptions ($p<.05$) based on Kruskal-Wallis analysis and post-hoc tests. Despite the higher rates of people receiving prescriptions in ABMUHB, that Health Board had an 8.4% (from 154.0 to 167.1 people per 1000 population) increase over the 11 years examined.

The smallest increase (2.3%, from 99.0 to 101.3 people per 1000 population) was noted in HDUHB although the fewest people receiving prescriptions were in WIMD4 areas of PTHB.

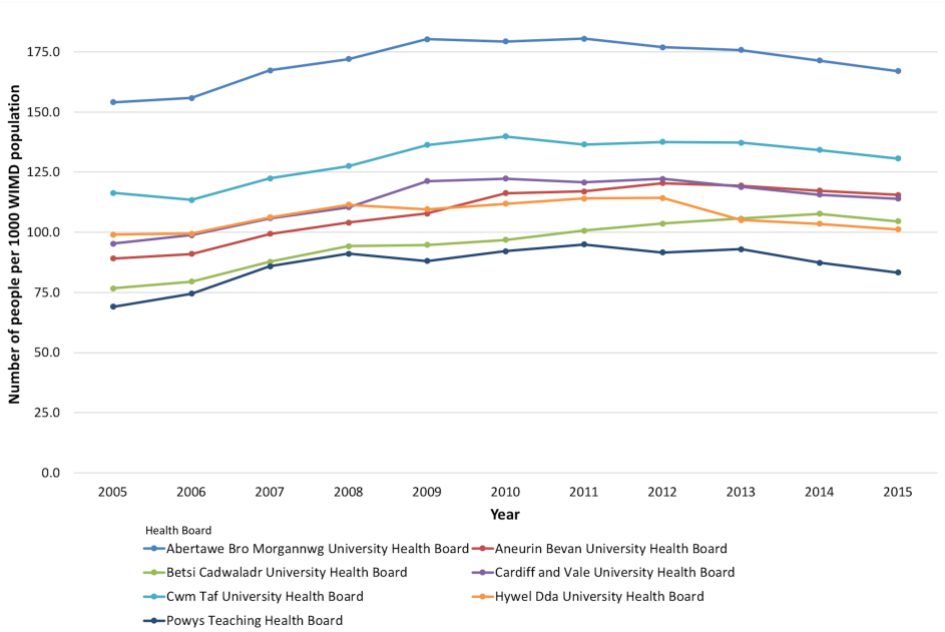


Figure I.8: Trend in the number of people receiving prescriptions for opioid medicines in the WIMD4 areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD4 areas in each Health Board

Kruskal-Wallis analysis of the difference in the number of people in the WIMD4 areas in each Health Board demonstrated a significant difference (Table I.11). Post-hoc tests showed 8 of 21 pairs of Health Board comparators were significantly different. The remaining pairs of Health Boards which were compared did not demonstrate significance.

Table I.11: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of people receiving opioid prescriptions being issued in WIMD4 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	.005*					
BCUHB	<.001*	>.999				
CVUHB	.049*	>.999	.321			
CTUHB	>.999	.443	.001*	>.999		
HDUHB	.001*	>.999	>.999	>.999	.158	
PTHB	<.001*	.082	>.999	.009*	<.001*	.246

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Betsi Cadwaladr University Health Board had the greatest number of people living in WIMD5 areas receiving opioid prescriptions in Wales between 2005 and 2015 (Table X). There was a significant difference (p<.001) between BCUHB and HDUHB which had the lowest numbers of people receiving prescriptions and saw a decline in those numbers (-10.5%, from31.5 to 28.2 people per 1000 population) over the same period.

The largest percentage increase in numbers (40.8%, from 75.8 to 106.7 people per 1000 population) were seen in PTHB however.

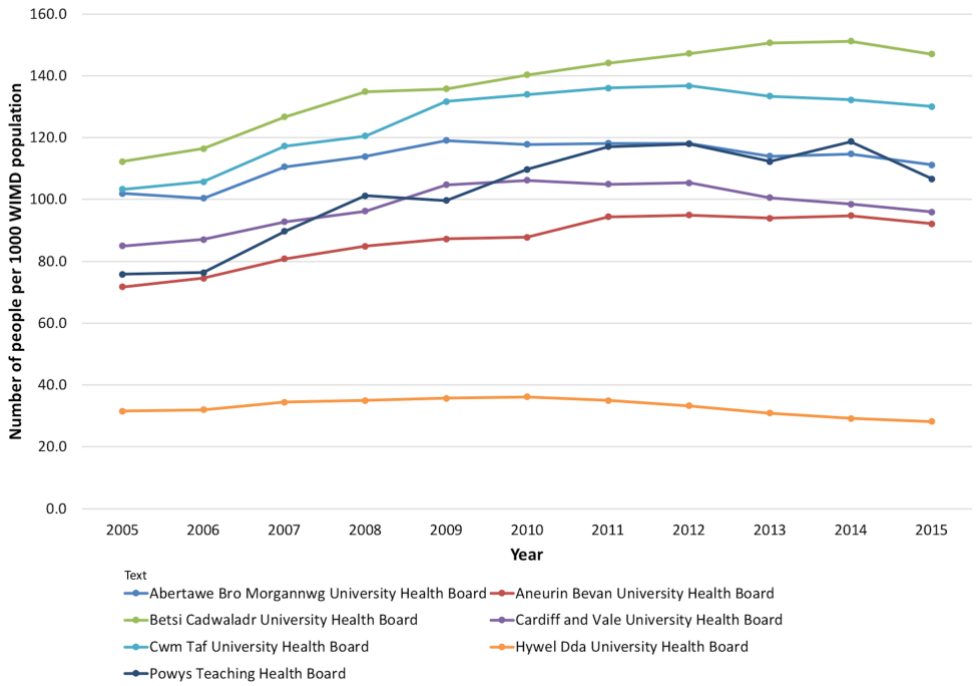


Figure I.9: Trend in the number of people receiving prescriptions for opioid medicines in the least deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD5 areas in each Health Board

Comparison of the numbers of people receiving prescriptions in WIMD5 areas in each Health Board demonstrated significant difference (p<.001). Post-hoc analysis revealed these differences predominated between HDUHB and 5 other Health Boards particularly (Table I.15).

Table I.12: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of people receiving opioid prescriptions being issued in WIMD4 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	.005*					
BCUHB	<.001*	>.999				
CVUHB	.049*	>.999	.321			
CTUHB	>.999	.443	.001*	>.999		
HDUHB	.001*	>.999	>.999	>.999	.158	
PTHB	<.001*	.082	>.999	.009*	<.001*	.246

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

I.3.1 Prescriptions by deprivation area

The trends in the number of prescriptions issued within each designated area of deprivation were similar to those of the numbers of people receiving them, across Wales.

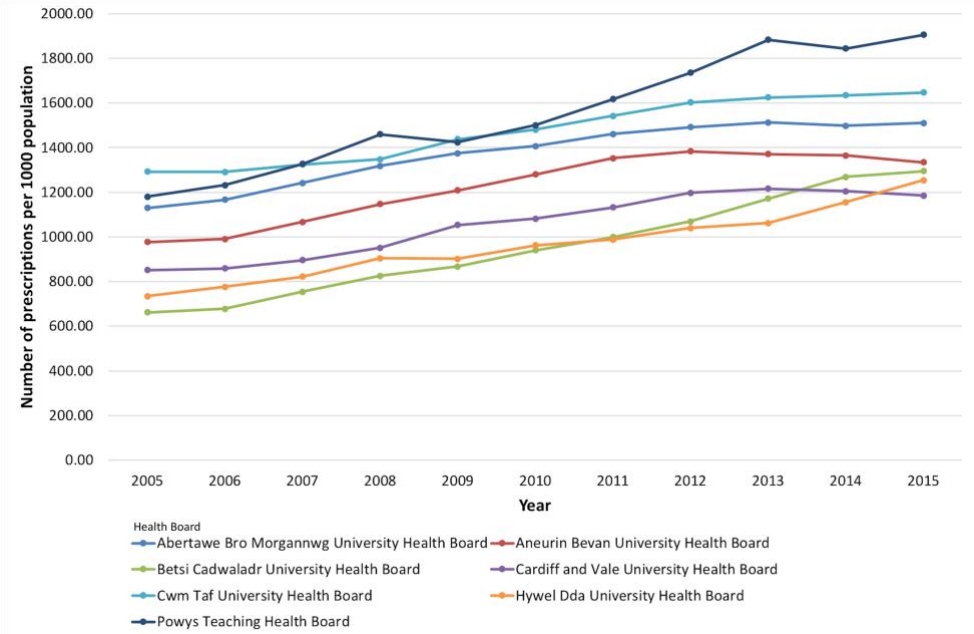


Figure I.10: Trend in the number of opioid prescriptions in the most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD1 areas in each Health Board

Powys Teaching Health Board had the highest number of prescriptions per 1000 population in WIMD1 areas, over the 11 years examined and experienced a 61.4% (from 1180.7 to 1905.7 prescriptions per 1000 population) increase in that time (Table I.15). The largest increase in the annual number of prescriptions issued in WIMD1 areas was in BCUHB (95.5%, from 662.0 to 1294.2 prescriptions per 1000 population).

Statistical differences were examined by Kruskal-Wallis and were significant ($p<.001$). Dunn's pairwise comparisons demonstrated significant differences between 8 of the 21 pairs of comparators (Table I.13).

Table I.13: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of opioid prescriptions being issued in WIMD1 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	>.999					
BCUHB	.007*	.582				
CVUHB	.055	>.999	>.999			
CTUHB	>.999	.626	<.001*	.003*		
HDUHB	.004*	.400	>.999	>.999	<.001*	
PTHB	>.999	.443	<.001*	.002*	>.999	<.001*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health

Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

In WIMD2 areas, there were much greater number of prescriptions issued in PTHB (median=1616.9) compared to the other Health Boards in Wales (Figure I.11). Over the study period, there was a 61.4% (from 1180.7 to 1905.7 prescriptions per 1000 population) increase.

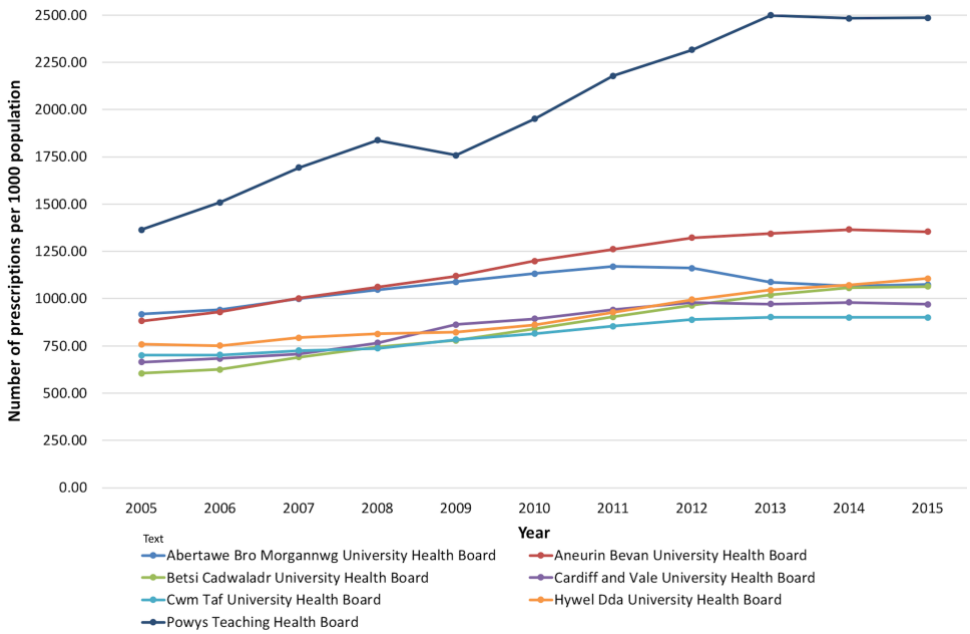


Figure I.11: Trend in the number of prescriptions for opioid medicines in the 2nd deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD2 areas in each Health Board

When compared to WIMD2 areas in other Health Boards by Kruskal-Wallis there were significant differences (p<.001), which following Dunn's pairwise comparison were demonstrated between 7 of the 21 pairs of comparators (Table I.14).

Table I.14: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of opioid prescriptions being issued in WIMD2 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	>.999					
BCUHB	.156	.041*				
CVUHB	.195	.053	>.999			
CTUHB	.021*	.004*	>.999	>.999		
HDUHB	.850	.285	>.999	>.999	>.999	
PTHB	.421	>.999	<.001*	<.001*	<.001*	<.001*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Table I.15: Trends in the annual number of opioid prescriptions in each Health Board in Wales by Welsh Index of Multiple Deprivation (WIMD) area. WIMD1=most deprived and WIMD5=least deprived area. Rate change over the 11-year study period included. Data population adjusted per Health Board (number of prescriptions per 1000 population)

	Health Board						
Number of prescriptions per 1000	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB
All opioids							
WIMD1							
2005	1129.4	977.0	662.0	851.2	1292.4	734.3	1180.7
2015	1510.3	1333.6	1294.2	1184.6	1646.1	1253.6	1905.7
Median	1406.2	1280.0	939.8	1082.2	1481.0	962.7	1616.9
Rate change 2005-2015 (%)	36.5	36.5	95.5	39.2	27.4	70.7	61.4
WIMD2							
2005	918.6	882.4	605.2	664.8	701.1	759.4	1364.5
2015	1073.9	1354.3	1064.3	970.7	901.2	1106.6	2486.0
Median	1073.9	1199.0	840.8	893.7	814.9	861.1	2179.3
Rate change 2005-2015 (%)	53.5	53.5	75.9	46.0	28.5	45.7	82.2
WIMD3							
2005	862.5	702.1	604.6	538.3	1014.1	655.7	774.6
2015	1135.8	1004.1	1037.2	802.9	1244.7	887.0	1010.8
Median	1039.1	905.4	840.0	715.1	1158.9	783.6	985.3
Rate change 2005-2015 (%)	31.7	43.0	71.5	49.2	22.7	35.3	30.5
WIMD4							
2005	770.5	466.6	362.1	462.9	628.0	560.9	300.3
2015	1035.5	731.5	642.1	679.6	830.2	735.3	488.7
Median	967.7	645.3	521.6	649.0	769.7	678.2	488.7
Rate change 2005-2015 (%)	34.4	56.8	77.3	46.8	32.2	31.1	62.8
WIMD5							
2005	470.6	343.7	494.9	373.4	486.5	166.8	309.4
2015	630.9	529.0	867.7	501.4	750.6	203.7	565.3
Median	581.3	452.8	698.2	492.8	698.4	180.2	558.8
Rate change 2005-2015 (%)	34.1	53.9	75.3	34.3	54.3	22.1	82.7

*ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

A different trend in prescribing was seen in WIMD3 areas (Table I.15) with the largest increase in the number of prescriptions issued occurring in BCUHB (75.9%, from 604.6 to 1037.2 prescriptions per 1000 population).

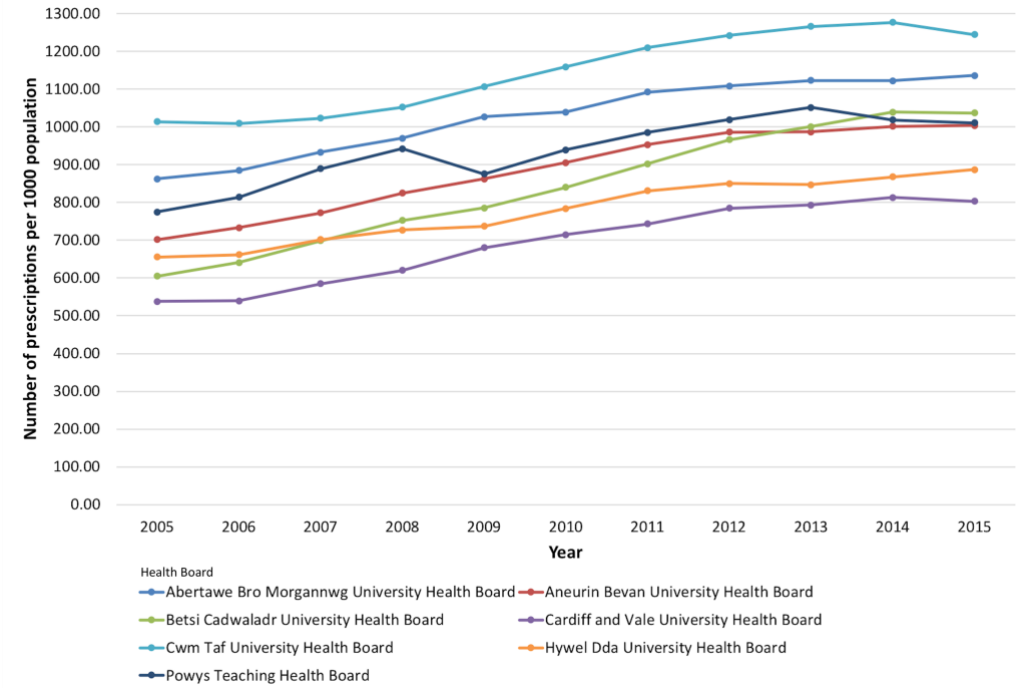


Figure I.12: Trend in the number of prescriptions for opioid medicines in the 3rd most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD3 areas in each Health Board

The largest number of prescriptions issued in WIMD3 areas was in CTUHB (median=1158.9) (Figure I.12) and that was also the Health Board which had the smallest increase (22.7%, from 1014.1 to 1244.7 prescriptions per 1000 population) over the 11 years examined. Cardiff and Vale University Health Board (median=715.1 prescriptions per 1000 population) had the lowest number of prescriptions issued in WIMD3 areas of any Health Board in Wales.

Table I.16: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of opioid prescriptions being issued in WIMD3 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	>.999					
BCUHB	.156	.041*				
CVUHB	.195	.361	>.999			
CTUHB	.021*	.004*	>.999	>.999		
HDUHB	.850	.285	>.999	>.999	>.999	
PTHB	.421	>.999	<.001*	.022*	<.001*	<.001*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Kruskal-Wallis test revealed a significant difference (p<.001) in the number of prescriptions issued in WIMD3 areas in the 7 Health Board. Dunn's pairwise

analysis highlighted 7 pairs of comparators where significant difference existed in the number of prescriptions (Table I.16).

Abertawe Bro Morgannwg University Health Board had the highest number of prescriptions issued in WIMD4 areas over the study and a 34.4% (from 770.5 to 1035.5 prescriptions per 1000 population) increase between 2005 and 2015 (Figure I.13).

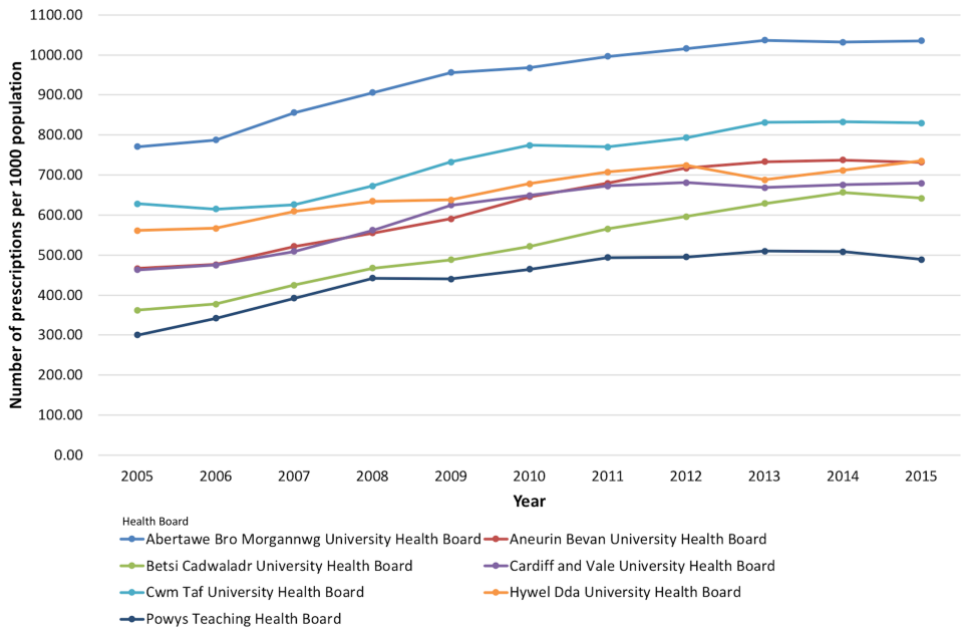


Figure I.13: Trend in the number of prescriptions for opioid medicines in the less deprived areas (WIMD4 as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD4 areas in each Health Board

The largest increase in annual prescription numbers was seen in BCUHB (77.3% increase, from 362.1 to 642.1 prescriptions per 1000 population) although that Health Board had around 49% fewer prescriptions issued in WIMD4 areas than ABMUHB.

As with previous analyses, there was an overall significance in the differences seen in the number of prescriptions issued in WIMD4 areas of each Health Board ($p<.001$) when determined by Kruskal-Wallis test. Post-hoc analysis confirmed significant differences existed between 7 of 21 pairs of comparators (Table I.17). The remaining pairs were not considered to have significant differences between them.

Table I.17: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of opioid prescriptions being issued in WIMD4 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	.011*					
BCUHB	<.001*	.041*				
CVUHB	.002*	>.999	>.999			
CTUHB	>.999	>.999	.014*	.757		
HDUHB	.072	>.999	.466	>.999	>.999	

PTHB	<.001*	.107	>.999	.371	<.001*	.017*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Two Health Boards, BCUHB (median=698.2 prescriptions per 1000 population) and CTUHB (median=698.4 prescriptions per 1000 population) had similar patterns of prescribing (Figure X) in the least deprived areas over the study period and with very similar median values, although a larger percentage increase was seen in BCUHB (Table X).

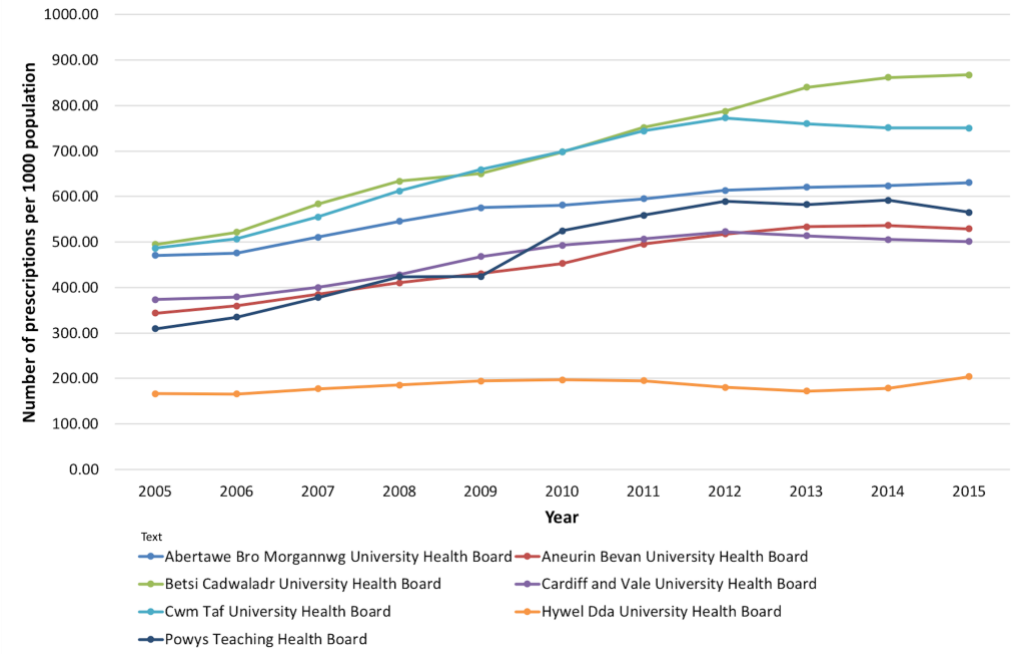


Figure I.14: Trend in the number of prescriptions for opioid medicines in the least deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD5 areas in each Health Board

The largest percentage increase in the annual number of prescriptions was in PTHB (82.7%, from 309.4 to 565.3 prescriptions per 1000 population) which had overall, the 4th highest level of prescribing during the study in the least deprived areas. Hywel Dda University Health Board had a lot fewer prescriptions in the least deprived areas than other Health Boards. Post-hoc statistical testing resulted in adjusted statistical significance between 4 of the 6 other Health Boards (Table I.18).

Table I.18: Dunn's pairwise comparison and Bonferroni post-hoc analysis of difference between the number of opioid prescriptions being issued in WIMD5 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	.830					
BCUHB	>.999	.011*				
CVUHB	.739	>.999	.009*			
CTUHB	>.999	.037*	>.999	.032*		
HDUHB	<.001*	.263	<.001*	.301	<.001*	

PTHB	>.999	>.999	.089	>.999	.256	.038*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Kruskal-Wallis test demonstrated the differences between the number of opioid prescriptions issued in WIMD5 areas across the 7 Health Boards were significant (p<.001). Further post-hoc analysis confirmed statistical differences between 8 of the 21 pairs of comparators (Table I.18).

I.3.2 Weak opioid prescribing by deprivation

There were similar trends in the number of weak opioid prescriptions that were issued across Wales, depending on the level of deprivation of the area in which the prescription was issued (Table I.19). In 2005, there were 77% more prescriptions issued in the most deprived areas of the Health Board with the highest level of prescribing (CTUHB, 1223.6 prescriptions per 1000 population) compared to the one with the least (BCUHB, 620.1 prescriptions per 1000 population). By 2015, the difference had reduced to 52% (PTHB, 1468.5 prescriptions per 1000 population versus CVUHB, 952.3 prescriptions per 1000 population).

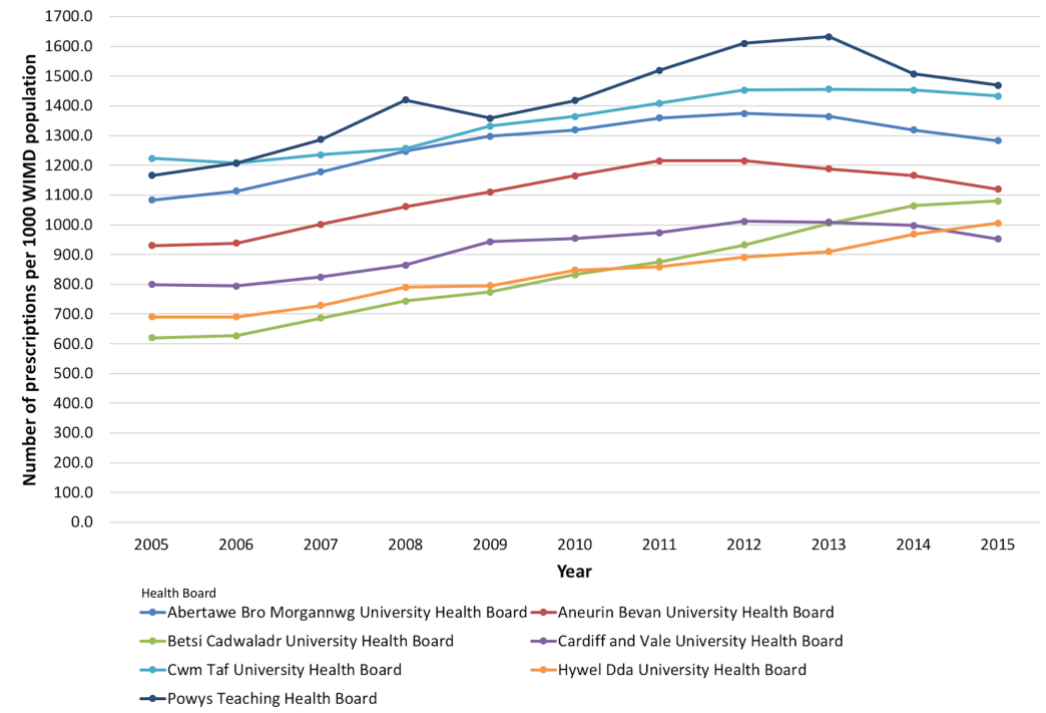


Figure I.15: Trend in the number of people receiving prescriptions for opioid medicines in the most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales. Data adjusted to population of WIMD1 areas in each Health Board

Table I.19: Trends in the annual number of weak opioid prescriptions in each Health Board in Wales by Welsh Index of Multiple Deprivation (WIMD) area

Number of prescriptions per 1000	Health Board						
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB
All opioids							
WIMD1							
2005	1082.9	930.4	620.1	798.7	1223.6	690.5	1165.3
2015	1282.6	1119.7	1079.9	952.3	1432.3	1005.9	1468.5
Median	1297.5	1119.7	831.9	952.3	1363.7	847.8	1419.7
Rate change 2005-2015 (%)	18.4	20.4	74.2	19.3	17.1	45.7	26.0
WIMD2							
2005	877.2	842.8	555.5	630.4	666.3	688.6	1325.9
2015	906.3	1135.5	896.2	791.2	801.8	882.4	2136.1
Median	984.2	1093.9	737.2	791.2	751.2	761.4	1826.4
Rate change 2005-2015 (%)	3.3	34.7	61.3	25.5	20.3	28.1	61.1
WIMD3							
2005	832.9	666.1	554.7	509.6	965.8	600.6	721.1
2015	964.7	866.4	853.7	651.8	1096.3	692.0	841.3
Median	975.6	836.4	631.2	631.2	1072.8	677.3	856.4
Rate change 2005-2015 (%)	15.8	30.1	53.9	27.9	13.5	15.2	16.7
WIMD4							
2005	735.8	441.0	334.1	431.8	590.7	516.9	280.7
2015	892.7	614.7	533.1	557.3	734.6	583.8	401.5
Median	895.1	578.1	450.4	556.1	708.9	569.6	401.5
Rate change 2005-2015 (%)	21.3	39.4	59.6	29.0	24.4	12.9	43.0
WIMD5							
2005	450.5	327.0	461.4	349.2	459.2	155.7	292.8
2015	545.8	458.8	716.2	419.7	672.1	165.9	481.1
Median	545.8	415.1	609.3	421.5	641.5	158.7	481.1
Rate change 2005-2015 (%)	21.2	40.3	55.2	20.2	46.4	6.5	64.3

*ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board WIMD1=most deprived and WIMD5=least deprived area. Rate change over the 11-year study period included. Data population adjusted per Health Board (number of prescriptions per 1000 population)

The greatest percentage increase in the annual number of weak opioid prescriptions issued within WIMD1 areas was in BCUHB (74.2%, from 620.1 to 1079.9 prescriptions per 1000 population) and the lowest was seen in CTUHB (17.1%, from 1223.6 to 1432.3 prescriptions per 1000 population). Powys Teaching Health Board saw an increase in the number of prescriptions of 26% (from 1165.3 to 1468.5 prescriptions per 1000 population) but had the largest overall numbers of prescriptions issued during the study period.

Statistical analysis demonstrated a significant difference in the number of weak opioid prescriptions issued in the WIMD1 areas of each Health Board ($p<.001$). Dunn's pairwise comparisons confirmed statistically significant differences between 9 of 21 pairs of comparators, the remaining 11 not being considered as significantly different (Table I.20).

Table I.20: Dunn's pairwise comparison post-hoc analysis of difference between the number of weak opioid prescriptions being issued in WIMD1 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	>.999					
BCUHB	.001*	.454				
CVUHB	021*	>.999	>.999			
CTUHB	>.999	.309	<.001*	.001*		
HDUHB	.001*	.309	>.999	>.999	<.001*	
PTHB	>.999	.098	<.001*	<.001*	>.999	<.001*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

In the second most deprived areas of Wales, PTHB had 51% more weak opioid prescriptions per 1000 population than the next highest prescribing Health Board in 2005 (Table I.19). The difference increased to 88% difference in 2015, although the trends in each Health Board were either slowing or declining from around 2012 onwards (Figure I.16). There was a 61.1% increase in the annual number of prescriptions in PTHB over the study period. The smallest percentage increase in WIMD2 weak opioid prescription numbers was in ABMUHB (3.3%, from 877.2 to 906.3 prescriptions per 1000 population).

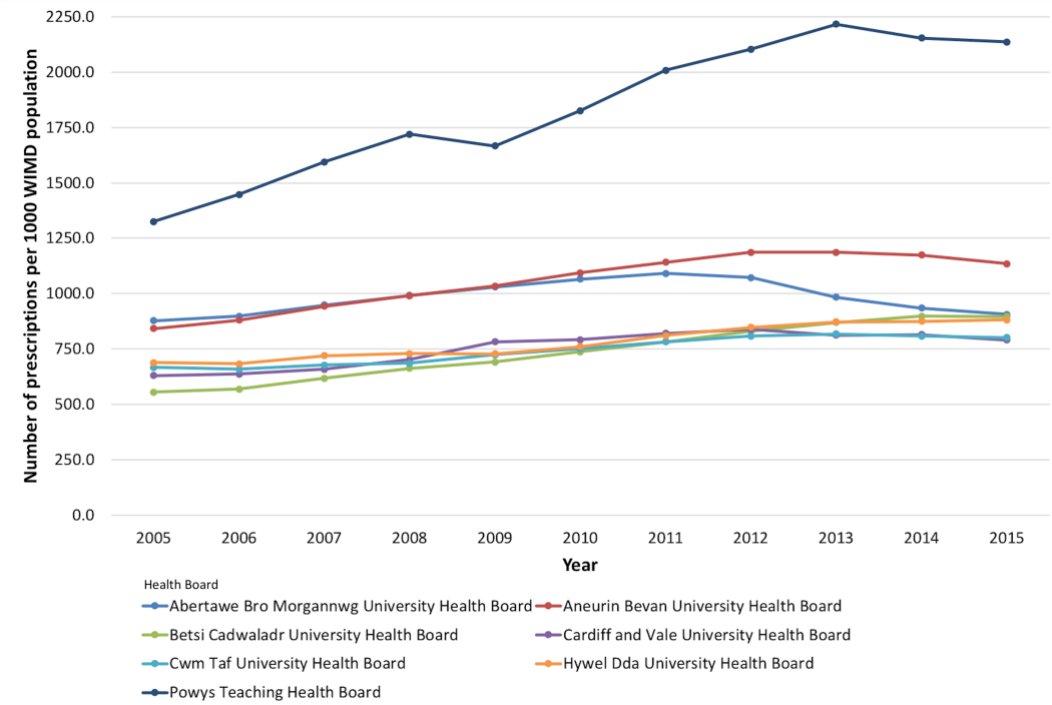


Figure I.16: Trend in the number of people receiving prescriptions for weak opioid medicines in the 2nd most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales
Data adjusted to population of WIMD2 areas in each Health Board

A Kruskal-Wallis test determined a statistically significant difference between the number of prescriptions issued in the WIMD2 areas of each Health Board across Wales. Post-hoc analysis confirmed significant differences between 11 of 21 pairs of comparators (Table I.21).

Table I.21: Dunn's pairwise comparison post-hoc analysis of difference between the number of weak opioid prescriptions being issued in WIMD2 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	>.999					
BCUHB	.025*	.006*				
CVUHB	.028*	.006*	>.999			
CTUHB	.012*	.002*	<.001*	>.999		
HDUHB	.139	.037*	>.999	>.999	<.001*	
PTHB	.953	>.999	<.001*	<.001*	<.001*	<.001*

*p <0.05 = statistically significant
**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Trends in the number of weak opioid prescriptions in WIMD3 areas across Wales were similar in most Health Boards, although there were approximately 36% fewer prescriptions per 1000 population issued overall, compared to the most deprived areas (WIMD1) over the study period (Table I.19).

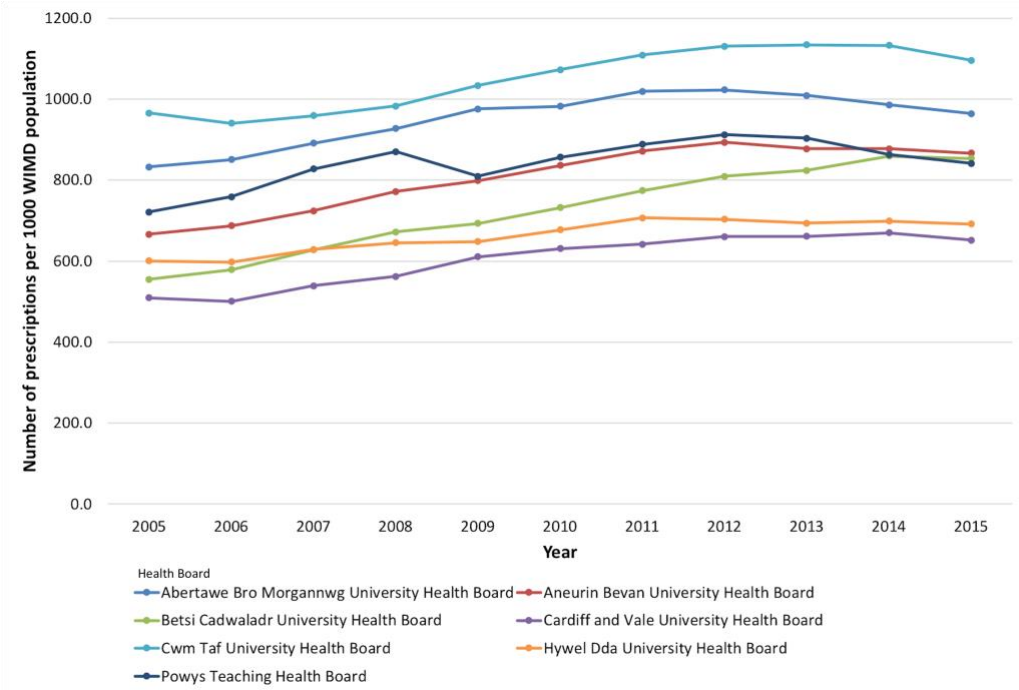


Figure I.17: Trend in the number of people receiving prescriptions for weak opioid medicines in the 3rd most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales
Data adjusted to population of WIMD3 areas in each Health Board

Cwm Taf University Health Board had the highest number of weak opioid prescriptions issued in WIMD3 areas between 2005 and 2015 but also had the smallest percentage increase (13.5%, from 965.8 to 1096.3 prescriptions per 1000 population) over that period. The largest percentage increase was seen in BCUHB (53.9%, from 554.7 to 853.7 prescriptions per 1000 population), which was consistent with the increases seen in the other areas of deprivation (Table I.19). Cardiff and Vale University Health Board had the lowest number of weak opioid prescriptions issued over the study period in WIMD3 areas.

Statistical analysis by Kruskal-Wallis test demonstrated a significant difference ($p<.001$) in the number of weak opioid prescriptions issued in WIMD3 areas in the 7 Health Boards across Wales. Dunn's pairwise comparison highlighted statistically significant differences between 9 of the 21 paired comparators.

Table I.22: Dunn's pairwise comparison post-hoc analysis of difference between the number of weak opioid prescriptions being issued in WIMD3 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	.793					
BCUHB	.011*	>.999				
CVUHB	<.001*	.035*	>.999			
CTUHB	>.999	.045*	<.001*	<.001*		
HDUHB	<.001*	.528	>.999	>.999	<.001*	
PTHB	>.999	>.999	>.999	.006*	.206	.135

*p <0.05 = statistically significant
**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

In the areas of lesser deprivation (WIMD4) across Wales, there were more than double the numbers of weak opioid prescriptions issued in ABMUHB (21.3% increase, from 735.8 to 892.7 prescriptions per 1000 population) (Figure I.17) which had the highest prescribing and PTHB (43.0% increase, from 280.7 to 401.5 prescriptions per 1000 population), which had the least.

As with the analysis of previous areas of deprivation, there was a significant difference between the number of weak opioid prescriptions issued in the 7 Health Boards (p<.001). Post-hoc analysis highlighted significant differences between ABMUHB and 5 of the 6 other Health Boards (Table I.23). There were significant differences between PTHB and three other Health Boards also (Table I.23).

Table I.23: Dunn's pairwise comparison post-hoc analysis of difference between the number of weak opioid prescriptions being issued in WIMD4 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	>.999					
BCUHB	<.001*	.421				
CVUHB	.001*	>.999	>.999			
CTUHB	>.999	>.999	.092	>.999		
HDUHB	.035*	>.999	.301	>.999	>.999	
PTHB	<.001*	.025*	<.001*	>.999	<.001*	.016*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

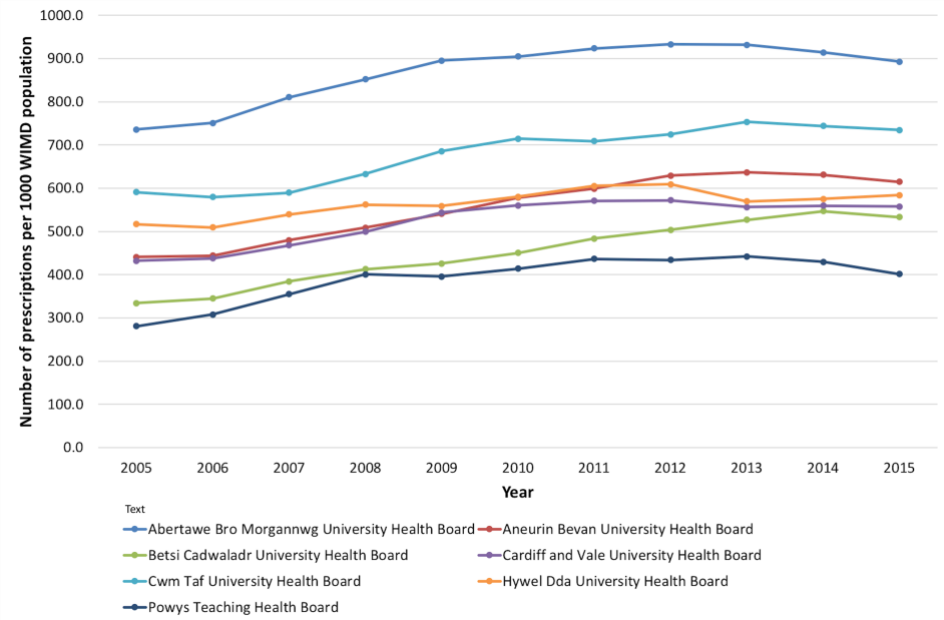


Figure I.18: Trend in the number of people receiving prescriptions for weak opioid medicines in the lesser deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales Data adjusted to population of WIMD4 areas in each Health Board

In 2005, there were nearly three times more weak opioid prescriptions issued in BCUHB (461.4 prescriptions per 1000 population), the Health Board with the highest rate of prescribing in the least deprived areas (WIMD5), compared to HDUHB (155.7 prescriptions per 1000 population) which had the least (Figure X). This rose to a 4.3 times difference in 2015 (716.2 versus 165.9 prescriptions per 1000 population respectively).

Hywel Dda University Health Board had the smallest percentage increase (6.5%, from 155.7 to 165.9 prescriptions per 1000 population) in prescribing of weak opioids in the least deprived areas. The highest percentage increase in the number of prescriptions issued was in PTHB (64.3%, from 292.8 to 481.1 prescriptions per 1000 population).

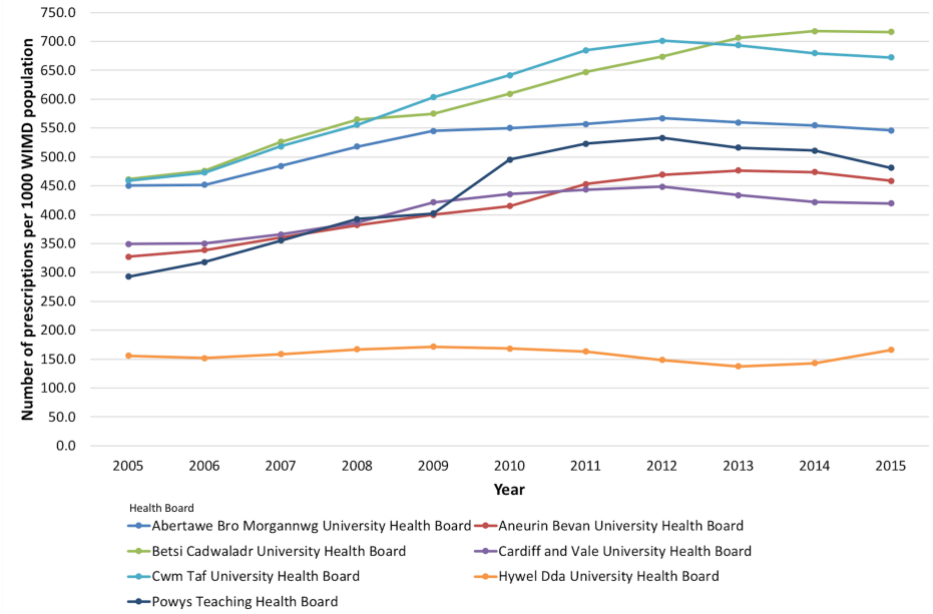


Figure I.19: Trend in the number of people receiving prescriptions for weak opioid medicines in the least deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales Data adjusted to population of WIMD5 areas in each Health Board

As with the other areas examined, there was a significant difference (p<.001) in the number of weak opioid prescriptions issued in WIMD5 areas of the 7 Health Boards. Dunn's pairwise comparison of 21 comparators confirmed significant differences between 8 pairs of Health Board areas.

Table I.24: Dunn's pairwise comparison post-hoc analysis of difference between the number of weak opioid prescriptions being issued in WIMD5 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB
ABUHB	.301					
BCUHB	>.999	.007*				
CVUHB	.120	>.999	.002*			
CTUHB	>.999	.012*	>.999	.004*		
HDUHB	<.001*	.343	<.001*	.775	<.001*	
PTHB	>.999	>.999	.072	>.999	.107	.048*

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

I.3.3 Strong opioid prescribing by deprivation

There were large percentage increases in the number of strong opioid prescriptions issued in all 5 deprivation areas across Wales. In the most deprived areas (WIMD1) PTHB (2739.2%, from 15.4 to 437.2 prescriptions per 1000 population) had the largest increase by some margin (Table I.25).

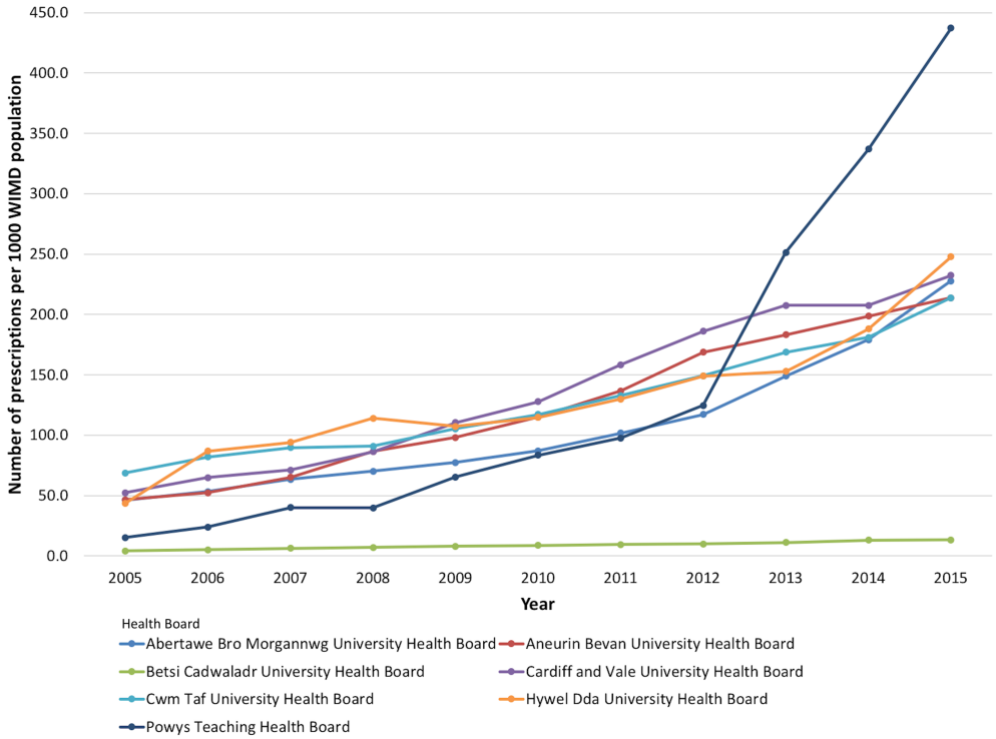


Figure I.20: Trend in the number of people receiving prescriptions for strong opioid medicines in the most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales
Data adjusted to population of WIMD1 areas in each Health Board

There was a comparatively low level of strong opioid prescribing in the WIMD1 areas of BCUHB, despite a tripling of the annual number of prescriptions in the 11 years examined (212.2% increase, from 4.3 to 13.4 prescriptions per 1000 population). In 2015, there were 32 times more strong opioid prescriptions per WIMD1 1000 population in PTHB compared to BCUHB (Figure I.20).

The remaining 5 Health Boards had similar levels of strong opioid prescribing over the study period (Table I.25).

Table I.25: Trends in the annual number of weak opioid prescriptions in each Health Board in Wales by Welsh Index of Multiple Deprivation (WIMD) area. WIMD1=most deprived and WIMD5=least deprived area. Rate change over the 11-year study period included

Number of prescriptions per 1000	Health Board						
	ABMUHB	ABUHB	BCUHB	CVUHB	CTUHB	HDUHB	PTHB
All opioids							
WIMD1							
2005	46.5	46.7	4.3	52.5	68.9	43.8	15.4
2015	227.7	213.9	13.4	232.3	213.8	247.7	437.2
Median	87.0	115.1	8.7	127.9	117.3	114.9	83.5
Rate change 2005-2015 (%)	390.1	358.3	212.2	342.5	210.5	466.2	2739.2
WIMD2							
2005	41.4	39.6	8.3	34.4	34.8	70.8	38.6
2015	167.6	218.8	18.6	179.5	99.4	224.1	349.9
Median	66.5	105.1	13.7	101.2	117.3	114.9	83.5
Rate change 2005-2015(%)	304.5	452.9	123.1	421.7	185.6	216.5	806.5
WIMD3							
2005	29.6	36.0	10.1	28.7	48.3	55.1	53.5
2015	171.1	137.6	25.7	151.2	148.4	195.0	169.5
Median	57.0	69.0	17.4	83.9	86.1	106.3	82.9
Rate change 2005-2015 (%)	477.0	282.2	153.7	426.6	207.4	253.7	216.9
WIMD4							
2005	34.7	25.6	12.3	31.0	37.2	44.1	19.5
2015	142.9	116.8	31.9	122.3	95.6	151.5	87.2
Median	63.1	67.2	24.4	88.6	59.9	97.7	50.7
Rate change 2005-2015 (%)	311.9	356.2	159.1	294.0	156.7	243.8	346.1
WIMD5							
2005	20.1	16.7	5.7	24.2	27.3	11.1	16.6
2015	85.1	70.2	17.6	81.7	78.5	37.8	84.2
Median	31.1	37.8	12.0	57.0	56.9	28.6	31.4
Rate change 2005-2015 (%)	322.7	321.3	209.8	237.7	187.5	241.1	406.4

*ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB = Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board. Data population adjusted per Health Board (number of prescriptions per 1000 population)

A Kruskal-Wallis test demonstrated a significant difference in the number of strong opioid prescriptions issued in the WIMD1 areas of each of the Health Boards. Dunn's pairwise comparison confirmed that the only statistically significant differences existed between BCUHB and the other 6 Health Boards.

Table I.26: Dunn's pairwise comparison post-hoc analysis of difference between the number of strong opioid prescriptions being issued in WIMD1 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	>.999					
BCUHB	.011*	.001*				
CVUHB	>.999	>.999	<.001*			
CTUHB	>.999	>.999	<.001*	>.999		
HDUHB	>.999	>.999	<.001*	>.999	>.999	
PTHB	>.999	>.999	.012*	>.999	>.999	>.999

*p <0.05 = statistically significant

**ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

A similar pattern in the number of strong opioid prescriptions issued in the second most deprived areas (WIMD2) in each Health Board to the most deprived areas was noted. As with the most deprived areas (WIMD1), BCUHB had the lowest rate of prescribing and the smallest percentage increase (123.1% increase, from 8.3 to 18.6 prescriptions per 1000 population) seen in any of the Health Boards.

There was a large increase in prescribing in PTHB with a particularly rapid rise from 2010 onwards. Overall, there was an 806.5% (from 38.6 to 349.9 prescriptions per 1000 population) increase in the annual number of strong opioid prescriptions issued in WIMD1 areas of PTHB

A statistically significant difference ($p<.001$) was noted in the number of strong opioid prescriptions issued in the WIMD2 areas across Wales. Post-hoc analysis however, confirmed statistically significant differences existed between 6 Health Boards and BCUHB, the remaining 15 comparisons were not significant (Table I.25).

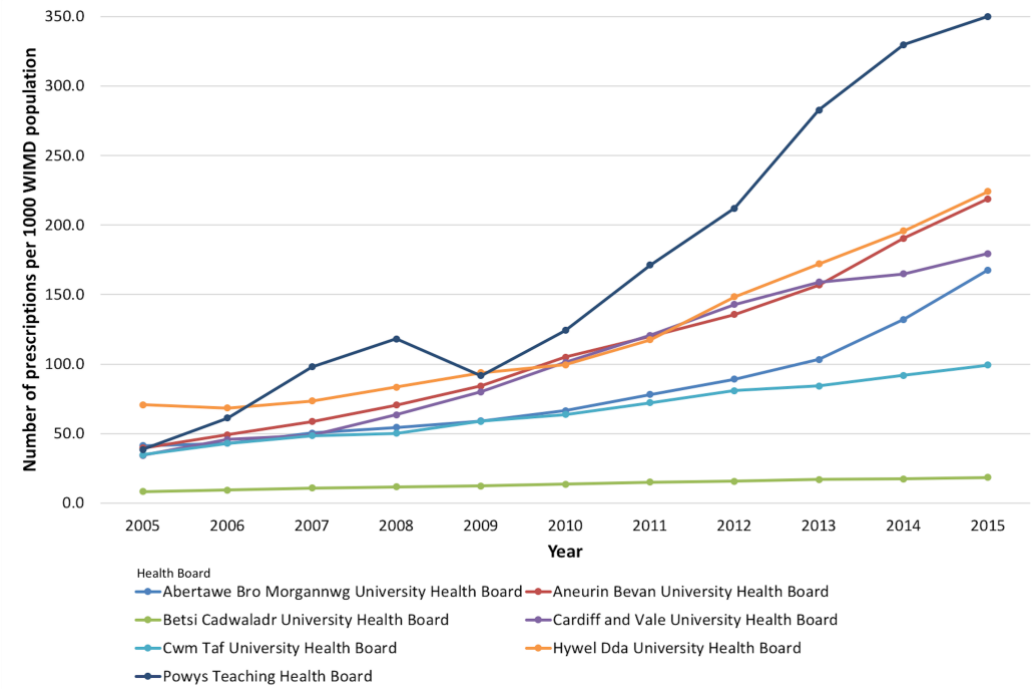


Figure I.21: Trend in the number of people receiving prescriptions for strong opioid medicines in the 2nd most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales
Data adjusted to population of WIMD2 areas in each Health Board

Table I.27: Dunn's pairwise comparison post-hoc analysis of difference between the number of strong opioid prescriptions being issued in WIMD2 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	>.999					
BCUHB	.030*	<.001*				
CVUHB	>.999	>.999	.001*			
CTUHB	>.999	>.999	.160	>.999		
HDUHB	>.999	>.999	<.001*	>.999	.656	
PTHB	.850	>.999	<.001*	>.999	.212	>.999

*p <0.05 = statistically significant **ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

In the areas of moderate deprivation (WIMD3), the highest rate of prescribing was in HDUHB (Figure I.21). The largest increase in the annual number of prescriptions was seen in ABMUHB however (477.0% increase, from 29.6 to 171.1 prescriptions per 1000 population).

The lowest rate of prescribing was again seen in BCUHB, which also had the lowest percentage increase in the annual number of prescriptions (153.7% increase, from 10.1 to 25.7 prescriptions per 1000 population) (Table I.25).

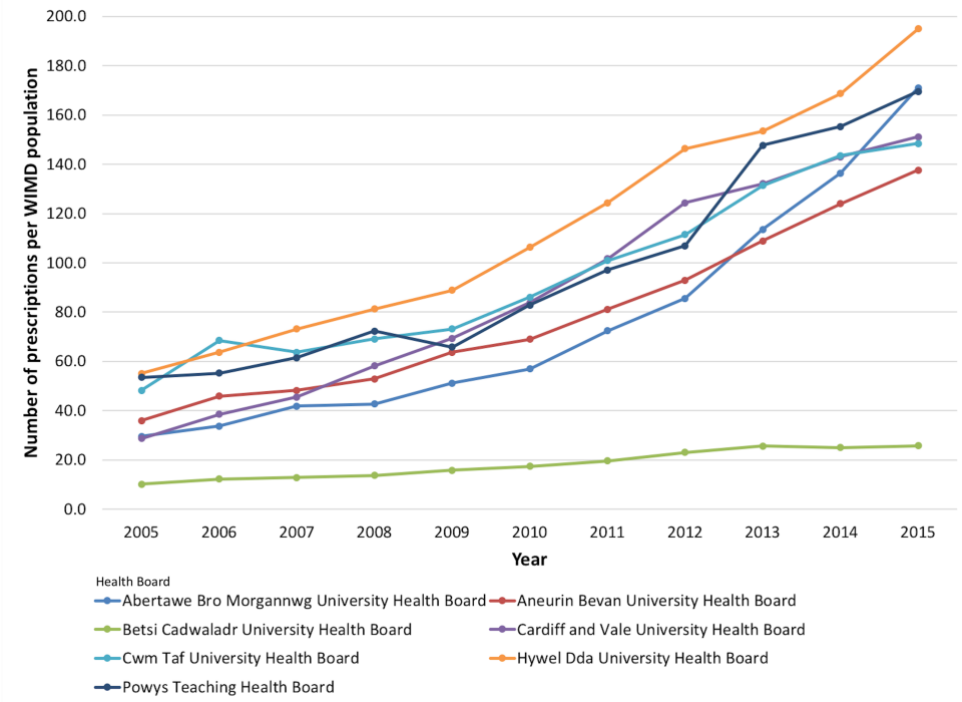


Figure I.22: Trend in the number of people receiving prescriptions for strong opioid medicines in the 3rd most deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales
Data adjusted to population of WIMD3 areas in each Health Board

The remaining 6 Health Boards had similar levels of prescribing in WIMD3 areas and this was reflected in the statistical analysis where Kruskal-Wallis demonstrated statistical significance (p<.001) but post-hoc analysis clarified significant differences existed between BCUHB and the 6 other Health Boards (Table I.28).

Table I.28: Dunn's pairwise comparison post-hoc analysis of difference between the number of strong opioid prescriptions being issued in WIMD3 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	>.999					
BCUHB	.033*	.015*				
CVUHB	>.999	>.999	.002*			
CTUHB	>.999	>.999	<.001*	>.999		
HDUHB	>.999	>.999	<.001*	>.999	>.999	
PTHB	1.00	>.999	<.001*	>.999	>.999	>.999

*p <0.05 = statistically significant **ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Hywel Dda University Health Board also had the highest rate of strong opioid prescribing in WIMD4 areas, which have lower overall levels of deprivation (Figure I.23). The highest percentage increase in the annual number of strong opioid prescriptions was in ABUHB (356.2%, from 25.6 to 116.8 prescriptions per 1000 population).

As with the more deprived areas, BCUHB had the lowest rates of strong opioid prescribing (Figure I.23) and a lower percentage increase in annual numbers of

prescriptions issued (159.1% increase, from 12.3 to 31.9 prescriptions per 1000 population) (Table I.25).

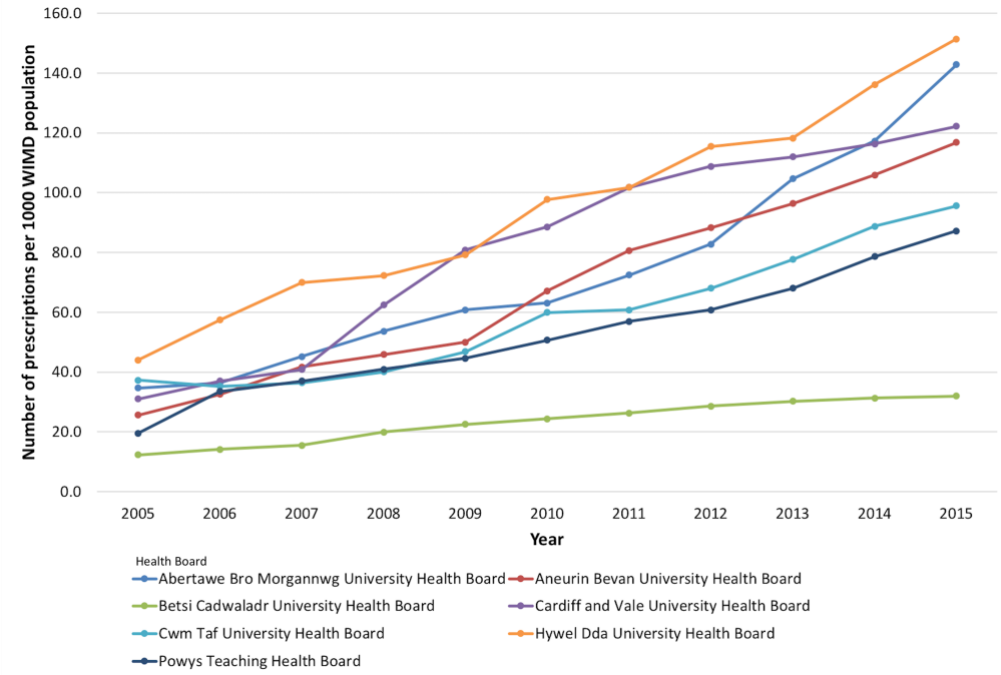


Figure I.23: Trend in the number of people receiving prescriptions for strong opioid medicines in the lesser deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales Data adjusted to population of WIMD4 areas in each Health Board

A Kruskal-Wallis test determined statistically significant differences (p<.001) between the number of strong opioid prescriptions issued in the WIMD4 areas in the 7 Health Boards. Dunn's pairwise comparison highlighted significant differences between BCUHB and 5 of the 6 other Health Boards. There was not a statistically significant difference between PTHB and BCUHB (p=.167) (Table I.29).

Table I.29: Dunn's pairwise comparison post-hoc analysis of difference between the number of strong opioid prescriptions being issued in WIMD4 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	>.999					
BCUHB	.001*	.005*				
CVUHB	>.999	>.999	<.001*			
CTUHB	>.999	>.999	.036*	>.999		
HDUHB	>.999	>.999	<.001*	>.999	.722	
PTHB	>.999	>.999	.167	>.999	>.999	.198

*p <0.05 = statistically significant **ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

The patterns of strong opioid prescribing in the least deprived areas of the Health Boards, were most different to those seen in the other areas of deprivation. However, the overall rates of prescribing in the least deprived areas were lower overall than in the other areas of deprivation (Table I.25).

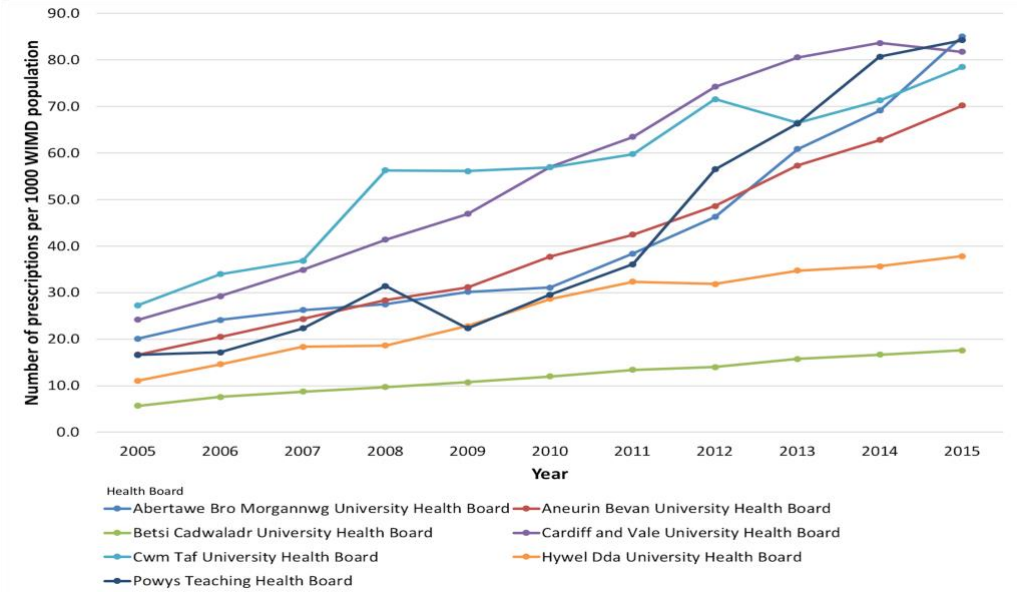


Figure I.24: Trend in the number of people receiving prescriptions for strong opioid medicines in the least deprived areas (as per Welsh Index of Multiple Deprivation (WIMD)) in each Health Board in Wales Data adjusted to population of WIMD5 areas in each Health Board

Whilst BCUHB remained the Health Board with the lowest rates of prescribing in all 5 areas of deprivation, PTHB was the Health Board with the highest percentage increase in the number of prescriptions issued in the 11 years examined (406.4%, from 16.6 to 84.2 prescriptions per 1000 population). Similar rates of strong opioid prescribing to those seen in PTHB, were seen in ABMUHB (Table X) where a large percentage increase in annual prescription numbers was seen (322.7%, from 20.1 to 85.1 prescriptions per 1000 population), particularly from 2012 (Figure I.24).

Table I.30: Dunn's pairwise comparison post-hoc analysis of difference between the number of strong opioid prescriptions being issued in WIMD5 areas by Welsh Health Board between 2005 and 2015

	Health Board**					
	ABMUHB	**ABUHB**	**BCUHB**	**CVUHB**	**CTUHB**	**HDUHB**
ABUHB	>.999					
BCUHB	.004*	.006*				
CVUHB	>.999	>.999	<.001*			
CTUHB	>.999	>.999	<.001*	>.999		
HDUHB	>.999	>.999	.554	.092	.092	
PTHB	>.999	>.999	.008*	>.999	>.999	>.999

*p <0.05 = statistically significant **ABMUHB = Abertawe Bro Morgannwg University Health Board; ABUHB = Aneurin Bevan University Health Board; BCUHB = Betsi Cadwaladr University Health Board; CVUHB = Cardiff and Vale University Health Board; CTUHB – Cwm Taf University Health Board; HDUHB = Hywel Dda University Health Board; PTHB = Powys Teaching Health Board

Statistical analysis using a Kruskal-Wallis test showed there was a significant difference (p<.001) in the number of strong opioid prescriptions issued in each Health Board. Post-hoc analysis however, confirmed that significant statistical difference was present between BCUHB and 5 other Health Boards (Table I.30). Differences between the other pairs of Health Boards that were compared, were not significant.

I.3.4 Log-linear regression

Split by LHB
LHB = 1
Rsquare is worse, 0.009, classification percentage is 86.7% which is high. Most influential factor is WIMD1, least influential factor is depression

Table I.31: Logistic regression for strong opioid prescribing in ABMUHB

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	WIMD1	.049	.005	103.329	1	<.001	1.050
	WIMD3	-.115	.004	747.369	1	<.001	.891
	WIMD4	-.103	.004	537.645	1	<.001	.902
	WIMD5	-.062	.005	160.378	1	<.001	.940
	Male	-.063	.003	443.156	1	<.001	.939
	DEPRESSION	-.410	.003	19220.547	1	<.001	.664
	Constant	2.102	.004	338243.005	1	<.001	8.185

a. Variable(s) entered on step 1: WIMD1, WIMD3, WIMD4, WIMD5, Male, DEPRESSION.

LHB2 = 1
85.7% classification correct
R square 0.015

Table I.32: Logistic regression for strong opioid prescribing in ABUHB

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	WIMD1	.022	.007	9.261	1	.002	1.022
	WIMD3	-.113	.005	532.942	1	<.001	.893
	WIMD4	-.093	.005	290.979	1	<.001	.911
	WIMD5	-.059	.010	33.584	1	<.001	.942
	Male	-.277	.004	5300.321	1	<.001	.758
	DEPRESSION	-.487	.004	15211.620	1	<.001	.614
	Constant	2.128	.004	223658.892	1	<.001	8.395

a. Variable(s) entered on step 1: WIMD1, WIMD3, WIMD4, WIMD5, Male, DEPRESSION.

Same conclusions as LHB1

LHB = 3
R-square 0.006
Classification 92.3%
WIMD3 most influential, depression least WIMD5 should be omitted

Table I.33: Logistic regression for strong opioid prescribing in BCUHB

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	WIMD1	-.058	.006	109.783	1	<.001	.944
	WIMD3	-.075	.007	119.045	1	<.001	.927
	WIMD4	-.145	.007	476.134	1	<.001	.865

	WIMD5	-.046	.006	60.189	1	<.001	.955
	Male	-.069	.004	354.612	1	<.001	.933
	DEPRESSION	-.426	.004	14256.663	1	<.001	.653
	Constant	2.194	.005	176920.239	1	<.001	8.971

a. Variable(s) entered on step 1: WIMD1, WIMD3, WIMD4, WIMD5, Male, DEPRESSION.

LHB = 4
R square = 0.01
Classification 87.3%

Table I.34: Logistic regression for strong opioid prescribing in CVUHB

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	WIMD1	-.034	.006	38.019	1	<.001	.967
	WIMD3	-.015	.007	4.840	1	.028	.985
	WIMD4	.013	.011	1.433	1	.231	1.013
	WIMD5	-.044	.009	22.650	1	<.001	.957
	Male	-.223	.005	2399.196	1	<.001	.800
	DEPRESSION	-.472	.005	10576.403	1	<.001	.624
	Constant	2.675	.005	270576.334	1	<.001	14.508

a. Variable(s) entered on step 1: WIMD1, WIMD3, WIMD4, WIMD5, Male, DEPRESSION.

WIMD 4 out
WIMD 3 highest, Depression lowest

LHB = 5
R square = 0.011
Classification 91.6%

Table I.35: Logisitic regression for strong opioid prescribing in CTUHB

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	WIMD1	-.050	.004	138.388	1	<.001	.951
	WIMD3	.074	.005	201.619	1	<.001	1.076
	WIMD4	-.169	.006	780.658	1	<.001	.844
	WIMD5	.064	.007	92.654	1	<.001	1.066
	Male	-.049	.003	205.111	1	<.001	.952
	DEPRESSION	-.321	.003	8458.097	1	<.001	.726
	Constant	2.378	.004	397735.485	1	<.001	10.785

a. Variable(s) entered on step 1: WIMD1, WIMD3, WIMD4, WIMD5, Male, DEPRESSION.

WIMD3 high influence, Depression lowest influence
LHB = 6
R square = 0.05
Classification = 90.3%

LHB = 7
R square = 0.005

Classification = 89.8
Most influential variable Male
Least Depression

Table I.36: Logistic regression for strong opioid prescribing in PTHB

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	WIMD1	-.065	.021	9.600	1	.002	.937
	WIMD3	-.233	.014	272.209	1	<.001	.792
	WIMD4	-.384	.013	827.583	1	<.001	.681
	WIMD5	-.062	.024	6.869	1	.009	.940
	Male	.117	.011	123.383	1	<.001	1.124
	DEPRESSION	-.397	.010	1449.612	1	<.001	.673
	Constant	2.465	.012	42092.408	1	<.001	11.769

a. Variable(s) entered on step 1: WIMD1, WIMD3, WIMD4, WIMD5, Male, DEPRESSION.

I.4 Abertawe Bro Morgannwg University Health Board

Over the course of 11 years, there was a 7.5% increase (from 74,488 to 80,050) in the annual number of people receiving prescriptions within all categorised deprivation areas – the smallest increase seen in Wales. When adjusted to the annual Health Board population over the same time, a 3.2% (from 153.7 to 159.7 people per 1000 population) increase was noted.

Table I.37: Annual change in the number of people per 1000 population receiving opioid prescriptions and annual change rate (percentage change) in Abertawe Bro Morgannwg University Health Board (ABMUHB)

	Welsh Index of Multiple Deprivation (WIMD)									
	1		2		3		4		5	
	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)
2005	192.5		160.5		159.1		154.0		101.9	
2006	193.9	0.7	163.0	1.6	157.6	-0.9	155.8	1.2	100.4	-1.5
2007	203.0	4.7	170.4	4.5	169.5	7.5	167.4	7.4	110.6	10.1
2008	207.1	2.0	176.1	3.4	172.7	1.9	172.1	2.8	113.9	3.0
2009	212.8	2.7	182.3	3.5	180.4	4.5	180.3	4.8	119.1	4.5
2010	211.8	-0.5	182.2	-0.1	177.4	-1.7	179.4	-0.5	117.8	-1.1
2011	213.6	0.8	183.6	0.8	180.3	1.6	180.5	0.6	118.2	0.4
2012	211.9	-0.8	179.5	-2.2	177.7	-1.4	177.0	-1.9	118.1	-0.1
2013	207.8	-2.0	166.4	-7.3	173.6	-2.4	175.8	-0.7	114.0	-3.5
2014	204.6	-1.5	158.3	-4.9	169.7	-2.2	171.4	-2.5	114.7	0.6
2015	198.8	-2.9	153.0	-3.4	166.3	-2.0	167.1	-2.5	111.2	-3.1
Overall rate change (%)	3.3		-4.7		4.5		8.4		9.1	

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

Statistically significant difference between areas of deprivation was noted by one-way ANOVA ($F(4, 50) = 168.6$, $p<.001$, $\eta^2 = 0.93$). Bonferroni post-hoc testing however, demonstrated that there was not a statistically significant difference between WIMD2 (mean = 170.5, SD = 10.9), WIMD3 (mean = 171.3, SD = 7.9) and WIMD4 areas (mean = 171.0, SD = 9.3, p = >.999).

The areas of least deprivation (WIMD-4 and WIMD-5) had the largest increases in numbers of people receiving prescriptions 8.4% (from 154.0 to 167.1 per 1000 population) and 9.1% (from 101.9 to 111.2 per 1000 population) respectively.

ABMUHB had 5,470,667 opioid prescriptions issued over 11 years, which accounted for 24.9% of recorded opioid prescriptions issued in categorised areas of Wales (22,001,509 total). This was population adjusted to 16.2% of opioid prescriptions issued in Wales.

The most deprived areas of ABMUHB had 35.6% (1,947,126) of all opioid prescriptions issued in that Health Board over the study period. This was 38% more prescriptions than were issued in the two least deprived categories of area (667,473 in WIMD-4 and 742,625 in WIMD-5 areas).

There were increases in opioid prescribing in all deprivation areas over the 11 years that the study examined although the 2.4 times difference between the number of prescriptions being issued in the most deprived areas versus the least, remained across the whole period (Table I.38).

There was the same difference in the number of weak opioid prescriptions per 1000 population seen between the most and least deprived areas in ABMUHB (Table I.38). The difference between the number of strong opioid prescriptions per 1000 population between the most deprived and least deprived areas of the Health Board increased from 2.3 times more in 2005 to 2.7 times larger in 2015 (Table I.38).

Table I.38: Changes in the number of opioid prescriptions issued by deprivation area within Abertawe Bro Morgannwg University Health Board between 2005 and 2015

	Number of prescriptions per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
All Opioids					
2005	1129.4	918.6	862.5	770.5	470.6
2015	1510.3	1073.9	1135.8	1035.5	630.9
Change rate (%)	33.7	16.9	31.7	34.4	34.1
Weak opioids					
2005	1082.9	877.2	832.9	735.8	450.5
2015	1282.6	906.3	964.7	892.7	545.8
Change rate (%)	18.4	3.3	15.8	21.3	21.2
Strong opioids					
2005	46.5	41.4	39.6	34.7	20.1
2015	227.7	167.6	171.1	142.9	85.1
Change rate (%)	390.1	304.5	477.0	311.9	322.7

Population adjusted data presented and change rate calculated between 2005 and 2015

Changes in the number of prescriptions issued for weak opioids were relatively modest with the greater increases seen in the least deprived areas. Strong opioid prescribing however appreciably increased in all areas although WIMD3 areas had the biggest growth over the study period.

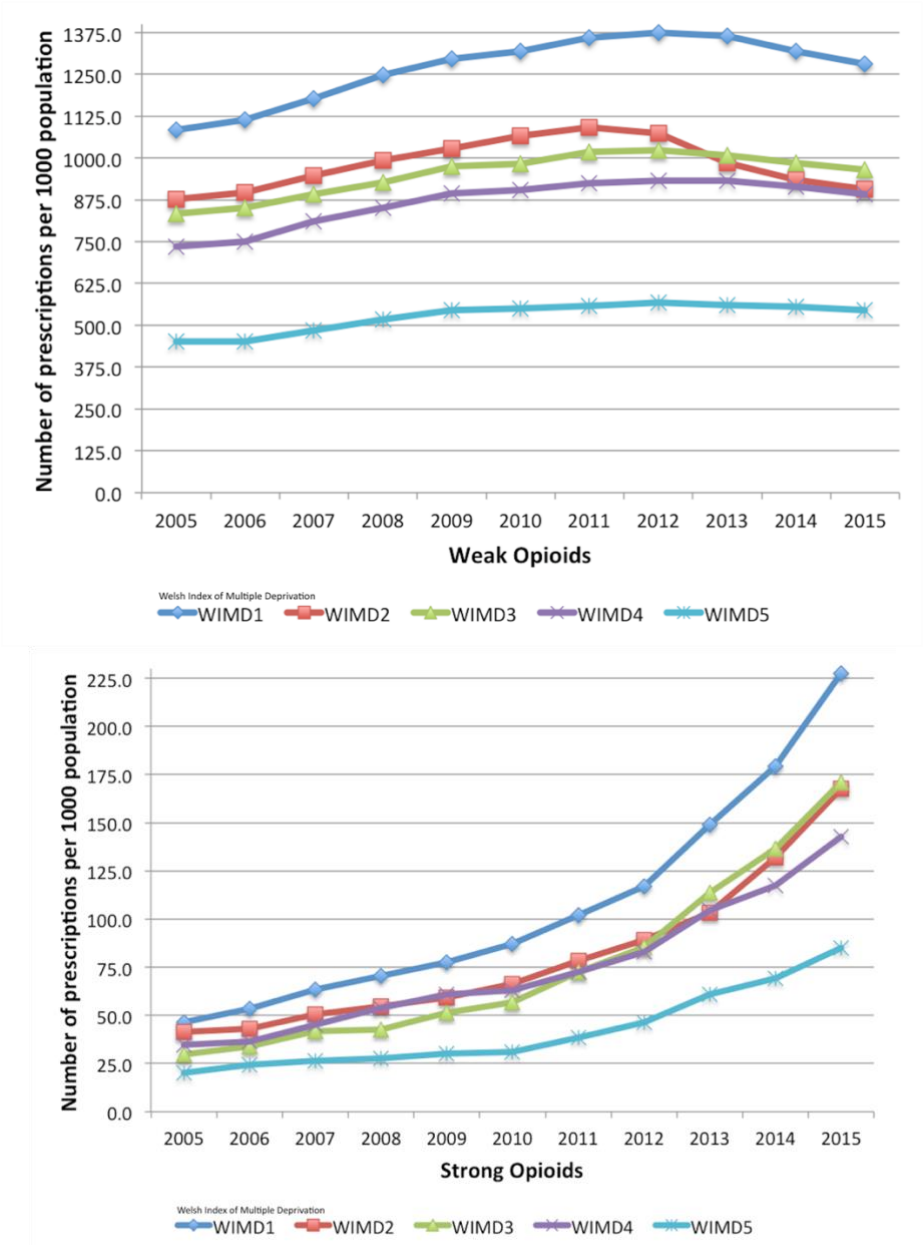


Figure I.25: Trends in the number of weak or strong opioid prescriptions issued per 1000 population in Abertawe Bro Morgannwg University Health Board by deprivation area (WIMD)
Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

I.5 Aneurin Bevan Local Health Board

There was a 23.5% (from 47,888 to 59,132) increase in the number of people receiving opioid prescriptions in the Health Board area of Aneurin Bevan. When adjusted to Health Board population, a 19.7% (from 121.3 to 145.2 people per 1000 population) increase was observed (Table I.39).

Table I.39: Annual change in the number of people per 1000 population receiving opioid prescriptions and annual change rate (percentage change) in Aneurin Bevan University Health Board (ABUHB)

	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)

2005	150.0		150.2		125.4		89.1		71.7	
2006	150.5	0.3	154.1	2.6	128.3	2.3	90.9	2.0	74.5	3.9
2007	161.0	7.0	164.8	7.0	137.1	6.8	99.3	9.2	80.8	8.5
2008	164.2	2.0	170.6	3.5	142.4	3.9	104.1	4.7	84.8	5.0
2009	168.9	2.9	175.9	3.1	145.2	2.0	107.8	3.6	87.3	2.9
2010	176.4	4.5	184.4	4.8	150.7	3.8	116.2	7.8	87.8	0.6
2011	177.5	0.6	186.9	1.3	151.7	0.7	117.0	0.7	94.4	7.5
2012	179.4	1.1	189.0	1.1	151.6	-0.1	120.5	3.0	94.9	0.6
2013	173.2	-3.4	188.9	0.0	149.8	-1.2	119.4	-0.9	93.9	-1.0
2014	172.4	-0.5	189.4	0.3	149.0	-0.5	117.3	-1.7	94.7	0.8
2015	169.6	-1.6	185.0	-2.4	145.5	-2.4	115.5	-1.5	92.1	-2.7
Change (%)	13.1		23.2		16.0		29.6		28.4	

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived

There were twice as many people receiving opioid prescriptions in the most deprived areas when compared to the least in 2005 (150.0 versus 71.7 people per 1000 population respectively). By 2015 the difference had reduced to result in 2.7 times more people in the most deprived areas receiving opioid prescriptions compared to the least deprived (17,963 versus 6,754).

Aneurin Bevan Local Health Board (ABLHB) issued 4,041,844 opioid prescriptions over the 11 year period examined, which equated to 18.4% of the total for Wales. This was population adjusted to 16.2% of prescriptions issued. Within the Health Board area, 34.9% (1,410,654) of all prescriptions issued were within the areas of highest deprivation compared to 9% in the areas of least deprivation (362,148 prescriptions).

Categories 3, 4 and 5 of the WIMD2011 scale accounted for 1,493,301 prescriptions between 2005 and 2015, which was only 6% more than the total prescribed within the most deprived areas of the Health Board.

Overall, there was a 50.3% (from 279,896 to 420,731) increase in the annual number of all opioid prescriptions in ABUHB between 2005 and 2015. Increases in the annual number of prescriptions were noted in all deprivation areas across ABUHB in that 11-year period.

In 2005, the number of weak opioid prescriptions issued in the areas of greatest deprivation in ABUHB was 2.9 times the number in the least deprived (Table I.40). There was a reduction in the difference over the 11 years examined to 2.4 times in 2015, although weak opioid prescribing continued to predominate in the areas of greater deprivation.

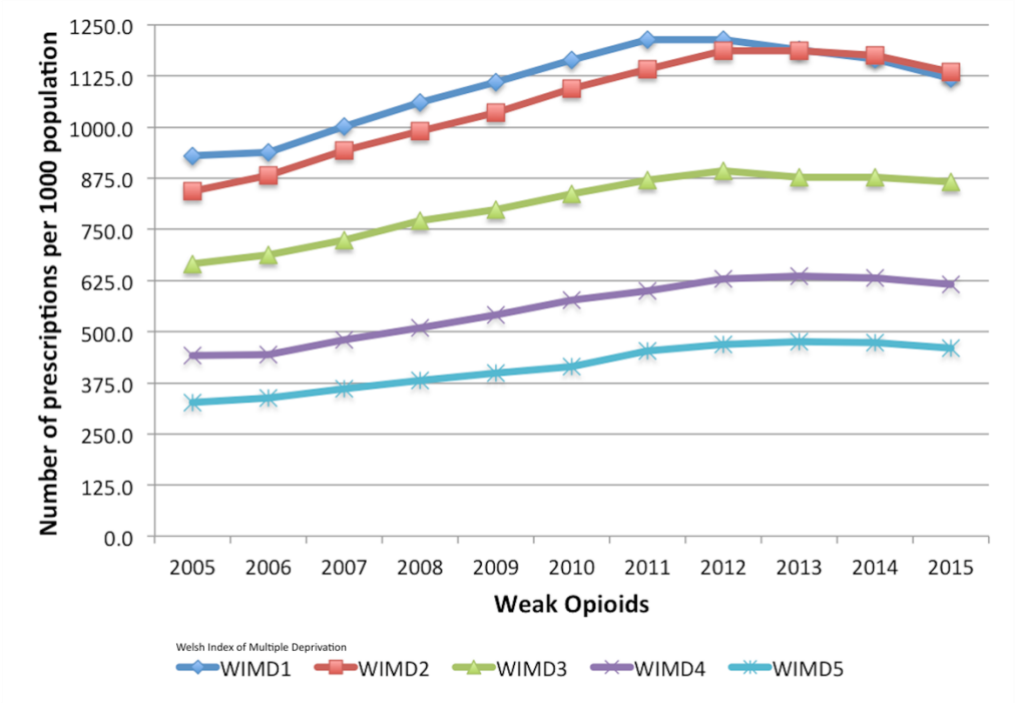
Table I.40: Changes in the number of opioid prescriptions issued by deprivation area within Aneurin Bevan University Health Board between 2005 and 2015

	Number of prescriptions per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
All Opioids					
2005	977.0	882.4	702.1	466.6	343.7
2015	1333.6	1354.3	1004.1	731.5	529.0
Change rate (%)	36.5	53.5	43.0	56.8	53.9

Weak opioids					
2005	930.4	842.8	666.1	441.0	327.0
2015	1119.7	1135.5	866.4	614.7	458.8
Change rate (%)	20.4	34.7	30.1	39.4	40.3
Strong opioids					
2005	46.7	39.6	36.0	25.6	16.7
2015	213.9	218.8	137.6	116.8	70.2
Change rate (%)	358.3	452.9	282.2	356.2	321.3

Population adjusted data presented and change rate calculated between 2005 and 2015

Strong opioid prescribing was higher in the more deprived areas of ABUHB also. The most deprived areas had 2.8 times more prescriptions issued in 2005 than the least deprived. There were significant increases in all areas, between 2005 and 2015 but the difference between most and least deprived also increased so that by 2015, there were three times more strong opioid prescriptions being issued in WIMD1 areas compared to WIMD5. The greatest increase, however, was seen in WIMD2 areas (Table I.40).



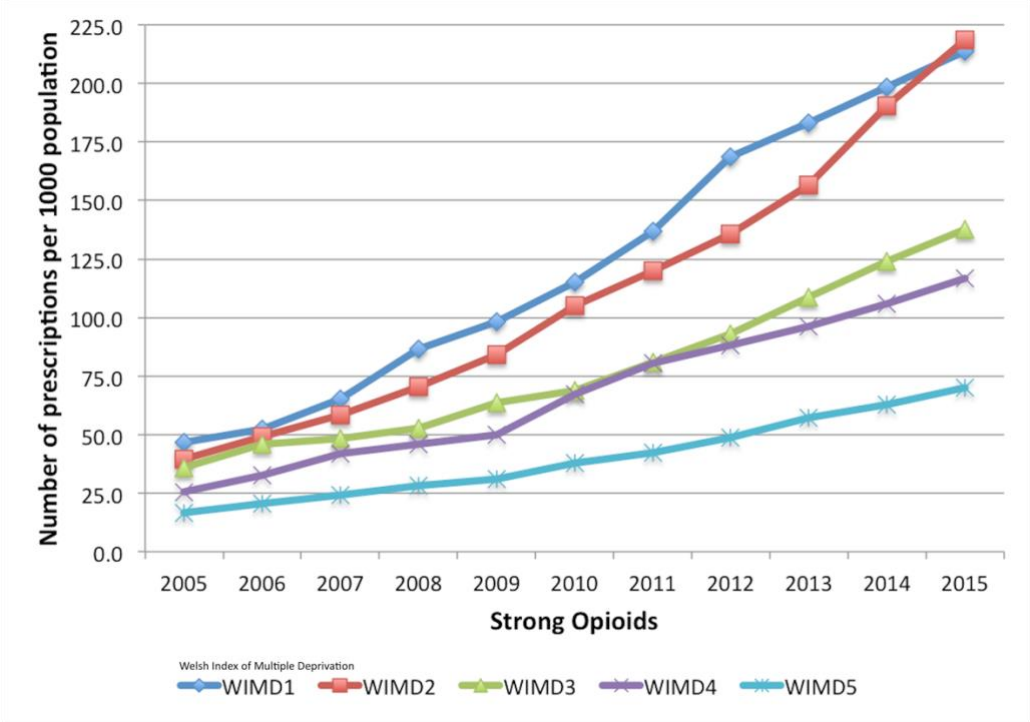


Figure I.26: Trends in the number of weak or strong opioid prescriptions issued per 1000 population in Aneurin Bevan University Health Board by deprivation area (WIMD)
Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

I.6 Betsi Cadwaladr University Health Board

In the eleven years studied, there was a 44.1% (from 54,464 to 78,483) increase in the annual number of people receiving any opioid prescription in all areas of Betsi Cadwaladr University Health Board (population adjusted to 35.5% increase). This was the highest increase seen in any Health Board in Wales over the 11 years of the study (Table I.41).

Table I.41: Annual change in the number of people per 1000 population receiving opioid prescriptions and annual change rate (percentage change) in Betsi Cadwaladr University Health Board (BCUHB)

	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)
2005	121.1		109.1		117.3		76.7		112.2	
2006	122.4	1.2	112.0	2.7	122.4	4.4	79.5	3.6	116.5	3.8
2007	131.3	7.2	121.9	8.8	133.6	9.1	87.7	10.4	126.7	8.8
2008	139.0	5.9	127.8	4.9	140.7	5.4	94.2	7.4	134.9	6.5
2009	142.9	2.8	130.9	2.4	143.6	2.0	94.7	0.6	135.8	0.7
2010	148.0	3.6	136.4	4.2	146.6	2.1	96.8	2.2	140.3	3.3
2011	152.7	3.1	140.1	2.7	149.8	2.2	100.7	4.0	144.1	2.7
2012	157.8	3.4	144.7	3.3	154.8	3.3	103.6	2.8	147.2	2.1
2013	167.7	6.2	148.6	2.7	158.2	2.2	105.7	2.0	150.7	2.4
2014	173.0	3.2	152.1	2.3	161.7	2.3	107.7	1.8	151.2	0.4
2015	168.5	-2.6	147.9	-2.7	156.8	-3.0	104.6	-2.8	147.0	-2.8
Change (%)	39.2		35.6		33.7		36.3		31.0	

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived

There was less difference in the annual number of people being issued opioid prescriptions between deprivation areas in BCUHB, other than WIMD4 area which maintained a 1.6 times difference in numbers compared to the most deprived area (WIMD1).

Nineteen percent of all opioid prescriptions in Wales (4,199,945 of 22,001,509) were issued within BCUHB between 2005 and 2015 (12.6% when adjusted to population). BCUHB demonstrated the largest increases in opioid prescribing of the seven Health Boards in Wales between 2005 and 2015. However, the least deprived areas (WIMD5) were not where the least prescriptions were issued. Instead WIMD4 areas were where the fewest prescriptions were issued per 1000 population (Table I.42).

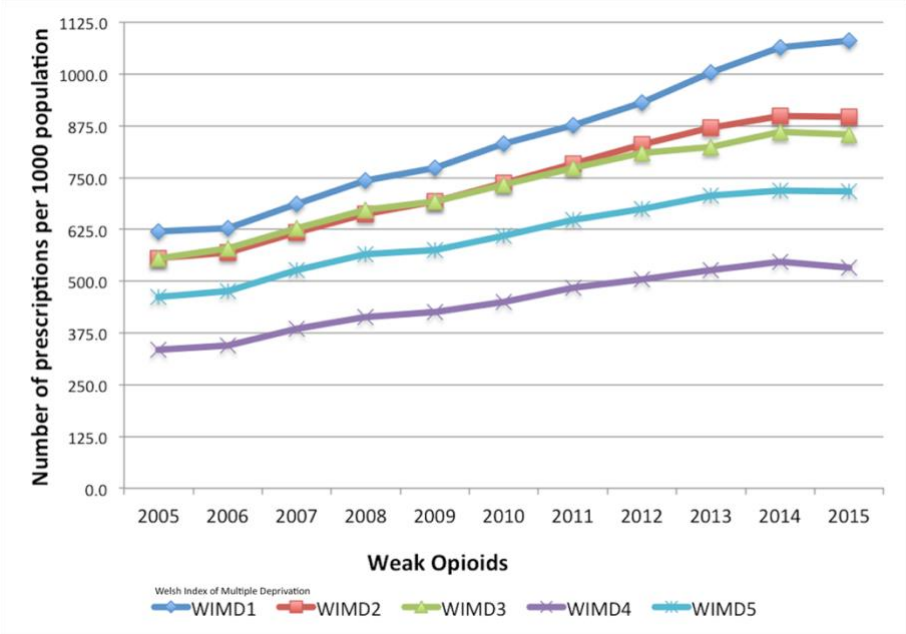
The increases in weak opioids were also greater than those seen in other Health Boards (Table I.42). More weak opioid prescriptions were issued in the most deprived areas of BCUHB than other areas. There were 1.8 times more weak opioid prescriptions per 1000 population issued in the most deprived areas of BCUHB compared to WIMD4 areas which had the least in 2005. Despite significant increases in all areas, the difference between WIMD1 and WIMD4 rose to 2 times by 2015 (Table I.42).

Table I.42: Changes in the number of opioid prescriptions issued by deprivation area within Betsi Cadwaladr University Health Board between 2005 and 2015

	Number of prescriptions per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
All Opioids					
2005	662.0	605.2	604.6	362.1	494.9
2015	1294.2	1064.3	1037.2	642.1	867.7
Change rate (%)	95.5	75.9	71.5	77.3	75.3
Weak opioids					
2005	620.1	555.5	554.7	334.1	461.4
2015	1079.9	896.2	853.7	533.1	716.2
Change rate (%)	74.2	61.3	53.9	59.6	55.2
Strong opioids				12.3	5.7
2005	4.3	8.3	10.1	31.9	17.6
2015	13.4	18.6	25.7	159.1	209.8
Change rate (%)	212.2	123.1	153.7		

Population adjusted data presented and change rate calculated between 2005 and 2015

Strong opioid prescribing was less prevalent in the most deprived areas of BCUHB than in WIMD4 areas – the opposite of weak opioid prescribing (Table I.42). However, there was a 212% increase (from 4.3 to 13.4 prescriptions per 1000 population) in WIMD1 areas between 2005 and 2015 (Figure I.27). There was a reduction in the difference between the number of strong opioid prescriptions in WIMD4 versus WIMD1areas over the study period, from 2.9 to 2.4 times more respectively.



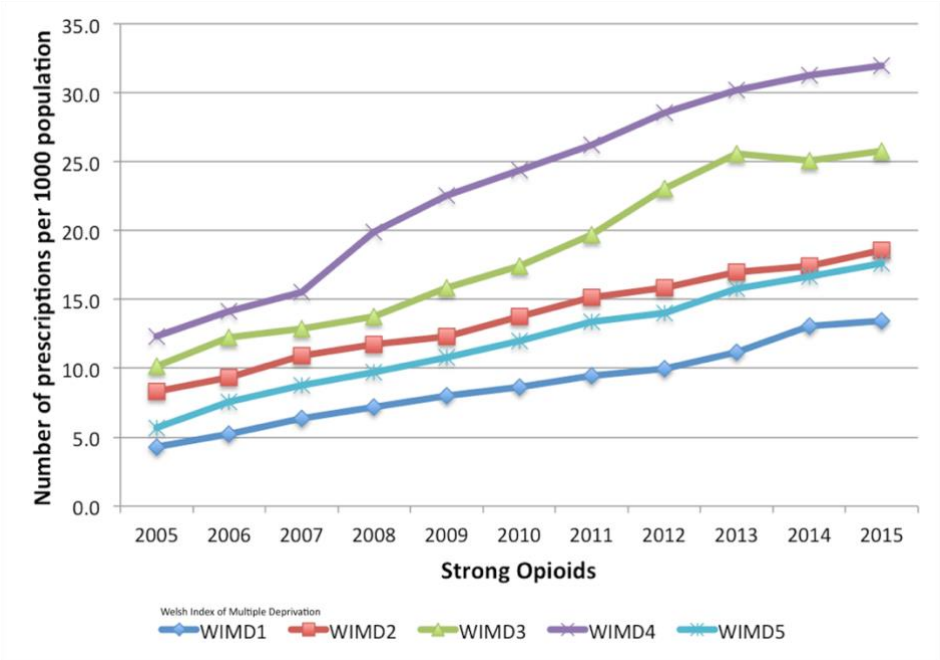


Figure I.27: Trends in the number of weak or strong opioid prescriptions issued per 1000 population in Betsi Cadwaladr University Health Board by deprivation area (WIMD)
Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

I.7 Cardiff and Vale University Health Board

The number of people receiving opioid prescriptions in the designated areas of CVUHB rose by 18% between 2005 and 2015 (from 40,891 to 48,367) or 15.7% (from 107.8 to 124.7 people per 1000 population) when adjusted to the population.

There was maintained throughout the 11 years examined, a 1.7 times difference between the numbers of people (per thousand) receiving opioid prescriptions in the most deprived areas compared to the least (Table I.43).

Table I.43: Annual change in the number of people per 1000 population receiving opioid prescriptions and annual change rate (percentage change) in Cardiff and Vale University Health Board (CVUHB)

	WIMD1		WIMD2		WIMD3		WIMD4		WIMD5	
	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)
2005	144.7		129.0		106.3		95.3		84.9	
2006	149.9	3.6	128.7	-0.2	106.2	-0.1	98.8	3.7	87.1	2.5
2007	154.4	3.0	136.1	5.7	113.6	7.0	105.8	7.0	92.8	6.5
2008	160.6	4.0	142.3	4.6	119.3	5.0	110.5	4.4	96.2	3.7
2009	172.6	7.5	154.0	8.2	127.9	7.2	121.3	9.8	104.7	8.9
2010	172.9	0.2	154.6	0.3	129.9	1.6	122.4	0.9	106.2	1.4
2011	172.0	-0.5	158.4	2.5	130.8	0.7	120.7	-1.3	104.9	-1.2
2012	176.3	2.5	162.5	2.6	131.2	0.3	122.3	1.3	105.3	0.4
2013	174.1	-1.3	157.2	-3.3	130.6	-0.5	118.9	-2.7	100.6	-4.5
2014	170.6	-2.0	159.2	1.3	130.1	-0.3	115.7	-2.7	98.5	-2.0
2015	163.6	-4.1	153.6	-3.5	128.2	-1.5	114.0	-1.5	95.9	-2.6
Change (%)	13.1		19.1		20.6		19.6		13.0	

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived

Whilst the most deprived areas in CVUHB had the highest number of people receiving opioid prescriptions, it was observed that those same areas had the lowest rate of increase over the study period. Deprivation areas WIMD2, 3 and 4 had similar rates of increase in the number of people receiving opioid prescriptions. However, there was around 26% difference in numbers between WIMD2 and WIMD4 areas (Table I.43).

Cardiff and Vale University Health Board (CVUHB) had 2,923,204 opioid prescriptions issued between 2005 and 2015, representing 13.3% of prescriptions in
Wales over that time (12.9% when adjusted to population).

Prescriptions issued within the most deprived areas of CVUHB accounted for 36.4% (1,064,009) of all prescriptions issued within that Health Board in the study period. The least deprived areas of CVUHB had the second highest number of prescriptions issued, 698,999 (23.9% of total). However, adjusted to the populations for those particular areas changed these proportions to 29% (WIMD1) and 12.6% (WIMD5) respectively.

Table I.44: Changes in the number of opioid prescriptions issued by deprivation area within Cardiff and Vale University Health Board between 2005 and 2015

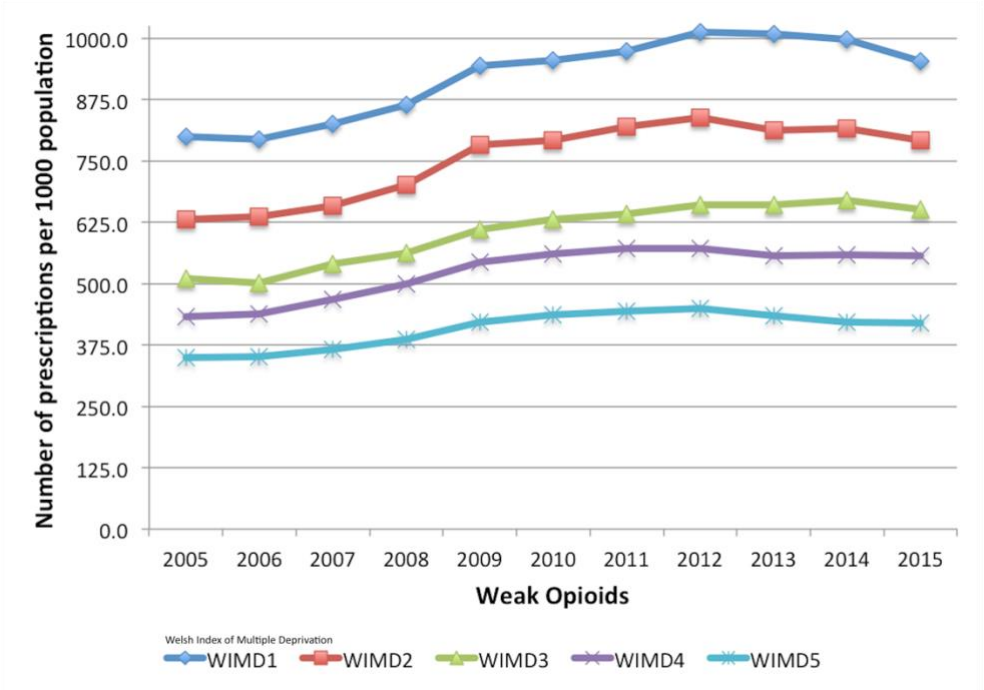
	Number of prescriptions per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
All Opioids					
2005	851.2	664.8	538.3	462.9	373.4
2015	1184.6	970.7	802.9	679.6	501.4
Change rate (%)	39.2	46.0	49.2	46.8	34.3
Weak opioids					
2005	798.7	630.4	509.6	431.8	349.2
2015	952.3	791.2	651.8	557.3	419.7
Change rate (%)	19.2	25.5	27.9	29.0	20.2
Strong opioids					
2005	52.5	34.4	28.7	31.0	24.2
2015	232.3	179.5	151.2	122.3	81.7

Change rate (%)	342.5	421.7	426.6	294.0	237.7

Population adjusted data presented and change rate calculated between 2005 and 2015

All deprivation areas had increases in the number of opioid prescriptions issued although there were marked differences in the number of prescriptions of weak and strong opioids in the most deprived areas compared the areas of least deprivation (Table I.44).

Weak opioid prescriptions were issued 2.3 times more often in the most deprived areas of CVUHB compared to the least deprived areas. The larger percentage increases in annual prescriptions numbers were however, seen in the WIMD areas 2 - 4 i.e. neither the most nor least deprived areas.
Strong opioid prescribing predominated in the areas of greater deprivation with more than double the number of prescriptions issues in the most deprived areas compared to the least deprived (Table I.44). This difference increased from 2.2 to 2.9 times more prescriptions per 1000 population between 2005 and 2015 (Figure I.28).



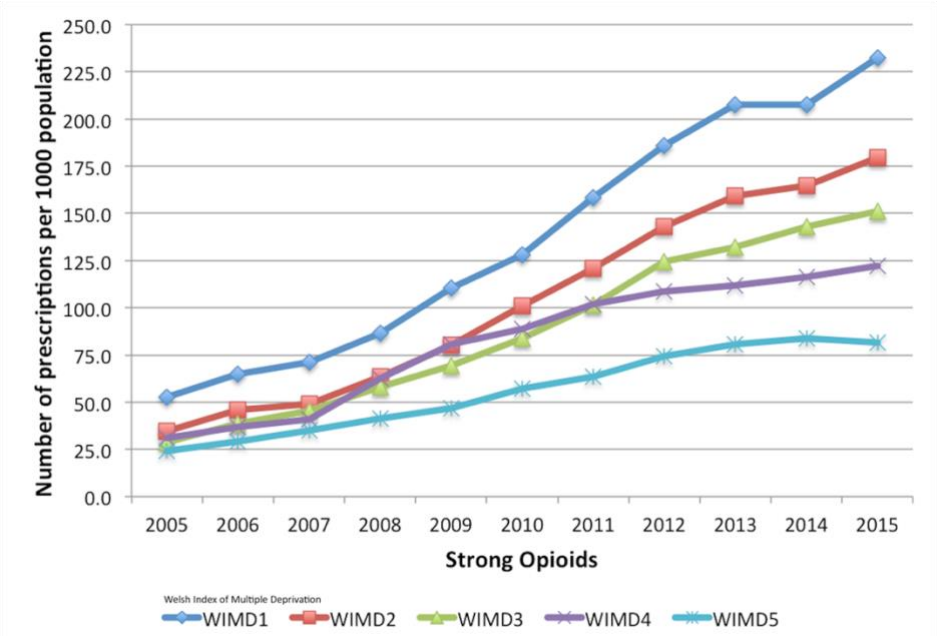


Figure I.28: Trends in the number of weak or strong opioid prescriptions issued per 1000 population in Cardiff and Vale University Health Board by deprivation area (WIMD)
Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

I.8 Cwm Taf University Health Board

There was a 13.7% increase in the number of people receiving opioid prescriptions each year in designated deprivation areas, across the whole of Cwm Taf University Health Board (CTUHB) between 2005 and 2015 (13.8% population adjusted increase).

Table I.45: Annual change in the number of people per 1000 population receiving opioid prescriptions and annual change rate (percentage change) in Cwm Taf University Health Board (CTUHB)

	Welsh Index of Multiple Deprivation (WIMD)									
	1		2		3		4		5	
	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)
2005	188.6		108.2		157.3		116.4		103.3	
2006	186.8	-0.9	107.9	-0.3	157.9	0.4	113.4	-2.6	105.8	2.4
2007	193.6	3.6	112.8	4.5	167.3	5.9	122.5	8.0	117.3	10.9
2008	199.1	2.9	114.8	1.8	171.4	2.5	127.6	4.2	120.6	2.8
2009	210.2	5.6	121.2	5.5	180.7	5.4	136.3	6.9	131.7	9.2
2010	209.6	-0.3	123.2	1.6	182.6	1.0	139.9	2.6	134.0	1.7
2011	214.1	2.1	127.6	3.6	191.8	5.0	136.6	-2.4	136.0	1.5
2012	217.4	1.6	130.0	1.9	192.1	0.1	137.5	0.7	136.8	0.6
2013	214.9	-1.2	127.5	-1.9	187.5	-2.4	137.3	-0.2	133.4	-2.5
2014	211.5	-1.6	124.4	-2.4	189.2	0.9	134.2	-2.2	132.2	-0.9
2015	210.4	-0.5	121.8	-2.1	181.2	-4.2	130.6	-2.7	130.1	-1.6
Change (%)	11.6		12.6		15.2		12.2		25.9	

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

The areas of CTUHB of least deprivation had the largest increase (25.9%, from 103.3 to 130.1 people per 1000) in the annual number of people receiving opioid prescriptions. However, there were 1.8 times more people receiving opioid

prescriptions in the most deprived areas compared to the least, in 2005, which changed to 1.6 times more in 2015 (Table I.45).

There was a peak in the number of people receiving opioid prescriptions in 2012, in all areas of CTUHB.

Cwm Taf Local Health Board had a total of 2,600,096 opioid prescriptions issued between 2005 and 2015; equivalent to 11.8% of the total issued in Wales during that time. This figure was 15.8% when adjusted to population. Prescribing increased by 28.8% (from 204,369 to 263,317) over the period examined. This was adjusted by population to 28.9% (from 893.9 to 1152.4 prescriptions per 1000 population) which, was the lowest percentage increase of any Health Board in Wales.

As with other Health Boards, the highest number of prescriptions was issued in the most deprived areas of CTUHB (Table I.46). The second highest area of prescribing was WIMD3 although these areas has around 25% fewer prescriptions issued than the most deprived areas during the study period.

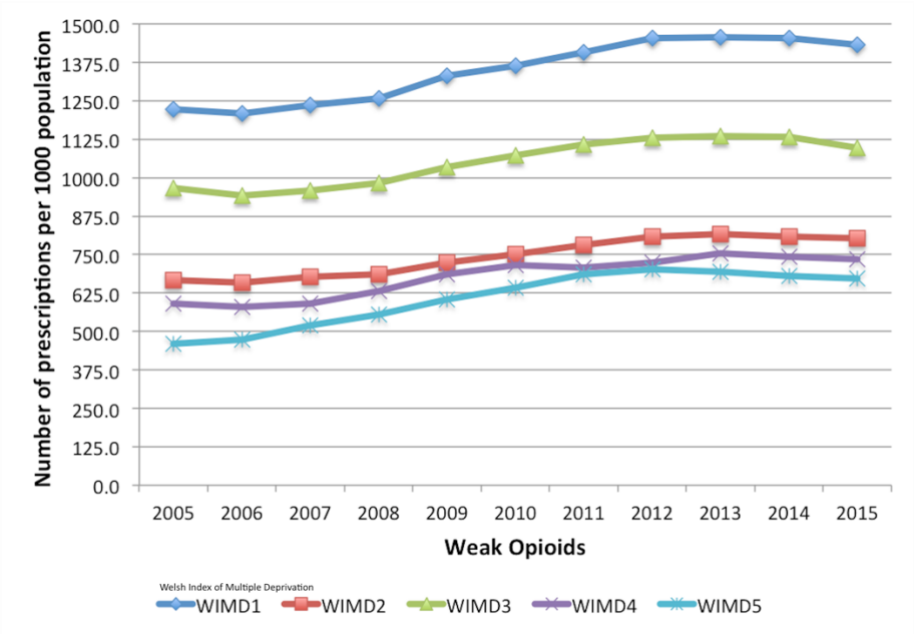
Table I.46: Changes in the number of opioid prescriptions issued by deprivation area within Cwm Taf University Health Board between 2005 and 2015

	Number of prescriptions per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
All Opioids					
2005	1292.4	701.1	1014.1	628.0	486.5
2015	1646.1	901.2	1244.7	830.2	750.6
Change rate (%)	27.4	28.5	22.7	32.2	54.3
Weak opioids					
2005	1223.6	666.3	965.8	590.7	459.2
2015	1432.3	801.8	1096.3	734.6	672.1
Change rate (%)	17.1	20.3	13.5	24.4	46.4
Strong opioids					
2005	43.8	70.8	55.1	44.1	11.1
2015	247.7	224.1	195.0	151.5	37.8
Change rate (%)	466.2	216.5	253.7	243.8	241.1

Population adjusted data presented and change rate calculated between 2005 and 2015

Weak opioid prescribing increased in all areas of CTUHB. The least deprived areas of the Health Board had the greatest increase in the number of weak opioid prescriptions issued although there were 2.6 times more prescriptions issued in the most deprived areas in 2005 which, changed to 2.2 times more in 2015 (Table I.46).

Strong opioid prescribing was highest in WIMD2 areas of CTUHB in 2005 (Table I.46). However, due to a significant increase (466.2%, from 43.8 to 247.7 prescriptions per 1000 population) in the most deprived areas, by 2015 the highest number of strong opioid prescriptions were being issued there. Although there was a substantial increase in the number of strong opioid prescriptions issued in the least deprived areas of CTUHB, there 6.6 times more prescriptions issued in the areas of highest prescribing in 2015 (Figure I.29).



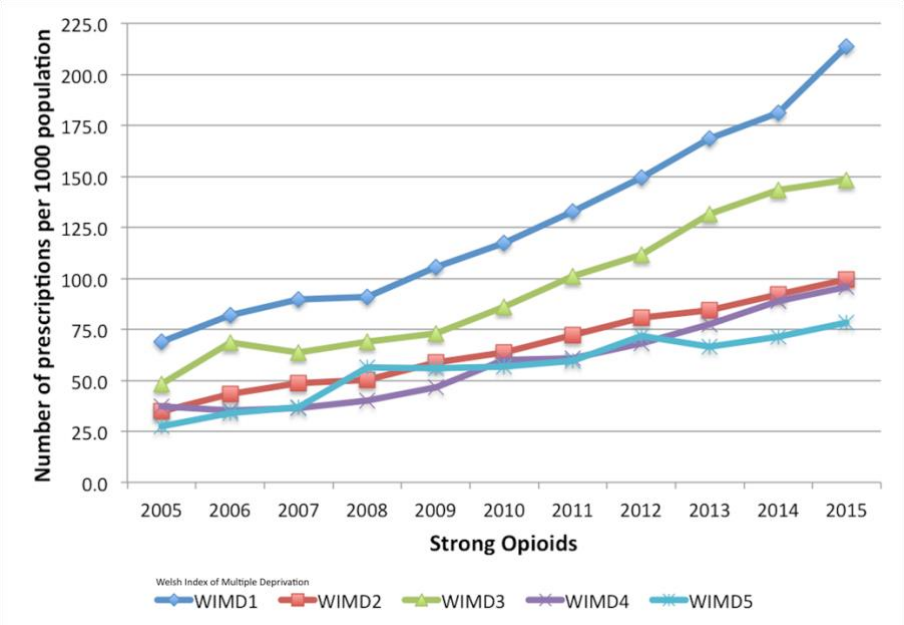


Figure I.29: Trends in the number of weak or strong opioid prescriptions issued per 1000 population in Cwm Taf University Health Board by deprivation area (WIMD)
Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

I.9 Hywel Dda Local Health Board

Hywel Dda LHB had a 15.6% increase in the annual number of people receiving opioid prescriptions between 2005 and 2015 (from 27,732 to 32,051). When adjusted to the annual Health Board population, this was 7.5% (from 96.1 to 103.3 people per 1000 population).

Table I.47: Annual change in the number of people per 1000 population receiving opioid prescriptions and annual change rate (percentage change) in Hywel Dda University Health Board (HDUHB)

	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5

	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)
2005	111.4		113.2		109.7		99.0		31.5	
2006	110.7	-0.6	112.6	-0.5	111.6	1.7	99.5	0.5	32.0	1.6
2007	114.8	3.7	120.1	6.7	115.7	3.6	106.3	6.8	34.5	7.7
2008	119.4	4.1	121.5	1.1	121.7	5.2	111.5	4.9	35.0	1.6
2009	119.6	0.2	121.7	0.2	119.1	-2.2	109.6	-1.7	35.7	1.9
2010	119.9	0.2	123.7	1.6	122.8	3.2	111.8	2.1	36.2	1.3
2011	124.6	3.9	124.0	0.2	124.0	1.0	114.0	2.0	35.0	-3.1
2012	122.7	-1.5	124.1	0.1	121.0	-2.4	114.3	0.2	33.3	-5.0
2013	124.1	1.1	126.7	2.1	119.5	-1.3	105.1	-8.1	30.9	-7.2
2014	128.0	3.1	126.9	0.2	119.5	0.0	103.5	-1.5	29.2	-5.6
2015	125.4	-2.0	127.8	0.7	119.6	0.1	101.3	-2.1	28.2	-3.3
Change (%)	12.6		12.9		9.0		2.3		-10.5	

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

The least deprived areas of Hywel Dda University Health Board saw a reduction in the numbers of people receiving opioid prescriptions over the study period. By 2015, there were 4.5 times more people receiving prescriptions in the areas of highest numbers (WIMD2) compared to the areas with the least population receiving prescriptions (Table I.47).

The areas which had the highest number of people to whom opioid prescriptions were issued (WIMD2), also had the higher increase in numbers between 2005 and 2015, 12.9% (from 113.2 to 127.8 people per 1000 population).

A total of 2,325,837 opioid prescriptions were issued within the Hywel Dda Local Health Board (HDLHB) area in the eleven years examined by this study. That figure corresponds to 10.6% of all opioid prescriptions in Wales or 11.4% when adjusted to the population.

The annual number of prescriptions issued in HDUHB rose 49.9% over the period (from 168,515 to 252,654). This was adjusted to 45.5% by population (from 2877.1 to 4186 prescriptions per 1000 population).

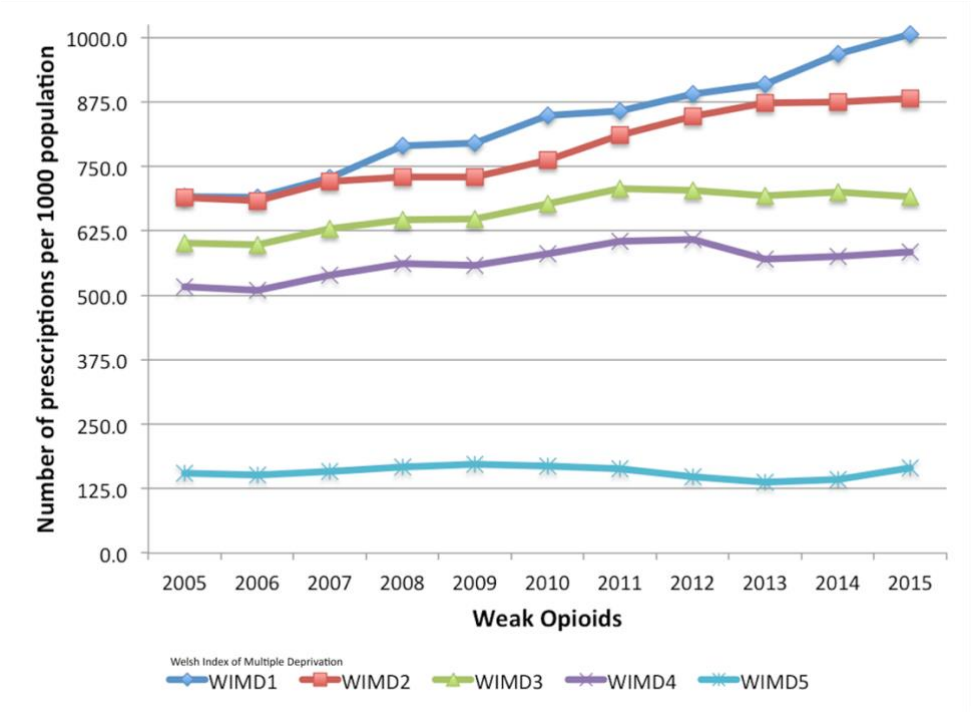
Table I.48: Changes in the number of opioid prescriptions issued by deprivation area within Cwm Taf University Health Board between 2005 and 2015

	Number of prescriptions per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
All Opioids					
2005	734.3	759.4	655.7	560.9	166.8
2015	1253.6	1106.4	887.0	735.3	203.7
Change rate (%)	70.7	45.7	35.3	31.1	22.1
Weak opioids					
2005	690.5	688.6	600.6	516.9	155.7
2015	1005.9	882.4	692.0	583.8	165.9
Change rate (%)	45.7	28.1	15.2	12.9	6.5
Strong opioids					
2005	43.8	70.8	55.1	44.1	11.1
2015	247.7	224.1	195.0	151.5	37.8
Change rate (%)	466.2	216.5	253.7	243.8	241.1

Population adjusted data presented and change rate calculated between 2005 and 2015

There were increases in weak opioid prescribing in all areas within HDUHB. The largest increase in prescribing was in the area of greatest deprivation (Table I.48) which also had 4 times the number of prescriptions issued in 2005 compared to the area with least number of prescriptions (WIMD5).

The annual number of weak opioid prescription rose least in the area of least deprivation. Subsequently, this led to a 6 times difference in the number of weak opioid prescriptions issued in the most deprived areas of HBUHB compared to the least deprived (Table I.48).



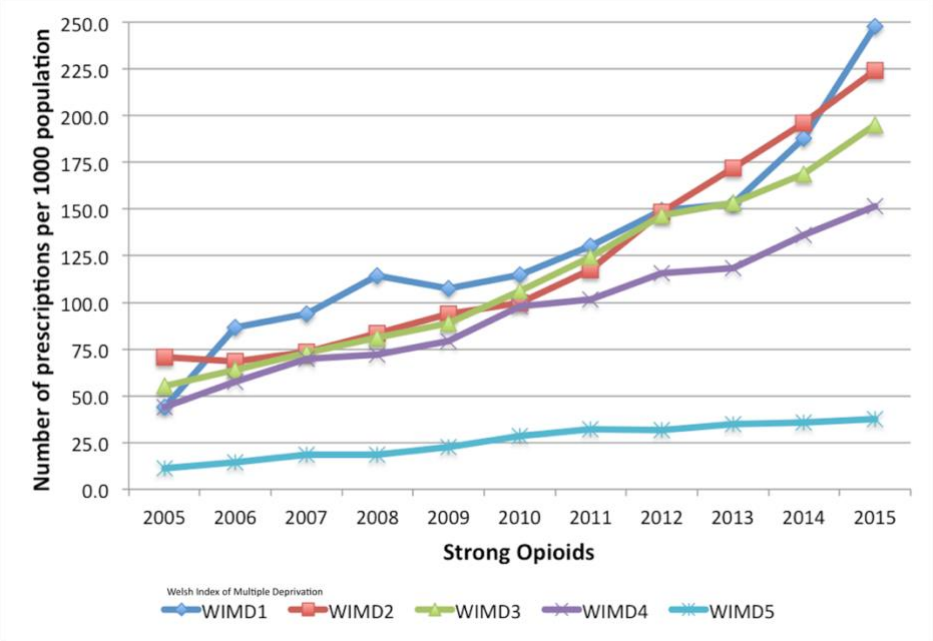


Figure I.30: Trends in the number of weak or strong opioid prescriptions issued per 1000 population in Hywel Dda University Health Board by deprivation area (WIMD)
Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

Strong opioid prescribing increased significantly in all areas of HDUHB but predominated in areas of greater deprivation levels. Prescribing in the areas of greatest deprivation were lower in 2005 than in three other categorised areas (WIMD2, 3 and 4). However, due to an increase in the number of annual prescriptions of 466.2% over the study period; by 2015 the number of prescriptions issued in the most deprived areas was the highest in the Health Board and 6.6 times more prescriptions than in the least deprived area where fewest prescriptions were issued (Figure I.30).

I.10 Powys Teaching Health Board

The predominantly rural Powys Teaching Health Board (PTHB) appeared, based on actual numbers of people, to have the fewest people in Wales receiving opioid prescriptions. There were 439,916 opioid prescriptions issued in PTHB during the period surveyed; 2% of the total in Wales. However, when adjusted to population this rose to 14.2% of people per 1000 population, which placed it above more populated Health Boards such as Betsi Cadwaladr and Cardiff and Vale.

Annual numbers of people rose 27.2% (from 5,712 to 7,272) over the 11 years or 13.9% (from 117.4 to 133.7 people per 1000) when adjusted to population.

Table I.49: Annual change in the number of people per 1000 population receiving opioid prescriptions and annual change rate (percentage change) in Powys Teaching Health Board (PTHB)

	Welsh Index of Multiple Deprivation (WIMD)									
	1		2		3		4		5	
	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)	People per 1000	Change rate (%)

2005	230.5		288.7		156.4		69.1		75.8	
2006	231.2	0.3	302.0	4.6	160.6	2.7	74.5	7.9	76.4	0.8
2007	247.5	7.0	321.3	6.4	172.3	7.3	85.9	15.2	89.7	17.4
2008	245.3	-0.9	342.6	6.6	179.1	3.9	91.1	6.0	101.2	12.8
2009	240.5	-2.0	320.9	-6.3	164.1	-8.4	88.1	-3.3	99.7	-1.5
2010	228.1	-5.2	326.2	1.7	167.6	2.1	92.2	4.7	109.8	10.1
2011	235.1	3.1	342.9	5.1	172.1	2.7	94.9	3.0	117.1	6.7
2012	252.3	7.3	364.5	6.3	176.5	2.6	91.7	-3.5	118.0	0.7
2013	259.2	2.7	374.7	2.8	173.3	-1.9	93.0	1.4	112.3	-4.8
2014	227.9	-12.1	343.2	-8.4	159.7	-7.8	87.3	-6.1	118.8	5.7
2015	227.6	-0.2	338.2	-1.5	159.	0.1	83.3	-4.6	106.7	-10.2
Change (%)	-1.3		17.1		2.2		20.5		40.8	

Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

More people residing in WIMD2 areas received prescriptions for opioids than those in the most deprived areas or those living WIMD4 areas where fewest people were issued prescriptions. Four times more people received prescriptions in the WIMD2 area compared to WIMD4 areas (Table I.49) across the study period. There was a small reduction in the annual number of people in the most deprived areas of PTHB receiving opioid prescriptions between 2005 and 2015 (Table I.49).

Powys Teaching Health Board had an increase of 77.1% (from 26,646 to 47,183) in annual opioid prescription numbers between 2005 and 2015. When adjusted to population, this was 58.6% (from 547.2 to 867.6 prescriptions per 1000), which was the second highest increase in Wales over the time period studied.

Although the most deprived areas of PTHB were not the areas with the highest numbers of prescriptions, there were more than 3 times the number of prescriptions issued in WIMD1 areas compared to WIMD5 (Table I.50).

Table I.50: Changes in the number of opioid prescriptions issued by deprivation area within Powys Teaching Board between 2005 and 2015

	Number of prescriptions per 1000				
	WIMD1	WIMD2	WIMD3	WIMD4	WIMD5
All Opioids					
2005	1180.7	1364.5	774.6	300.3	309.4
2015	1905.7	2486.0	1010.8	488.7	565.3
Change rate (%)	61.4	82.2	30.5	62.8	82.7
Weak opioids					
2005	1165.3	1325.9	721.1	280.7	292.8
2015	1468.5	2136.1	841.3	401.5	481.1
Change rate (%)	26.0	61.1	16.7	43.0	64.3
Strong opioids					
2005	15.4	38.6	53.5	19.5	16.6
2015	437.2	349.9	169.5	87.2	84.2
Change rate (%)	2739.2	806.5	216.9	346.1	406.4

Population adjusted data presented and change rate calculated between 2005 and 2015

The largest increase in the annual number of weak opioid prescriptions issued in Powys occurred in the least deprived areas (Table I.50). A similar increase, however, was seen in the annual number of weak opioid prescriptions issued in WIMD2 areas, the areas of highest overall prescription numbers. The areas with

the highest number of prescriptions issued (WIMD2) had 1.5 times more prescriptions than the next nearest area (WIMD1) of higher prescribing in 2015.

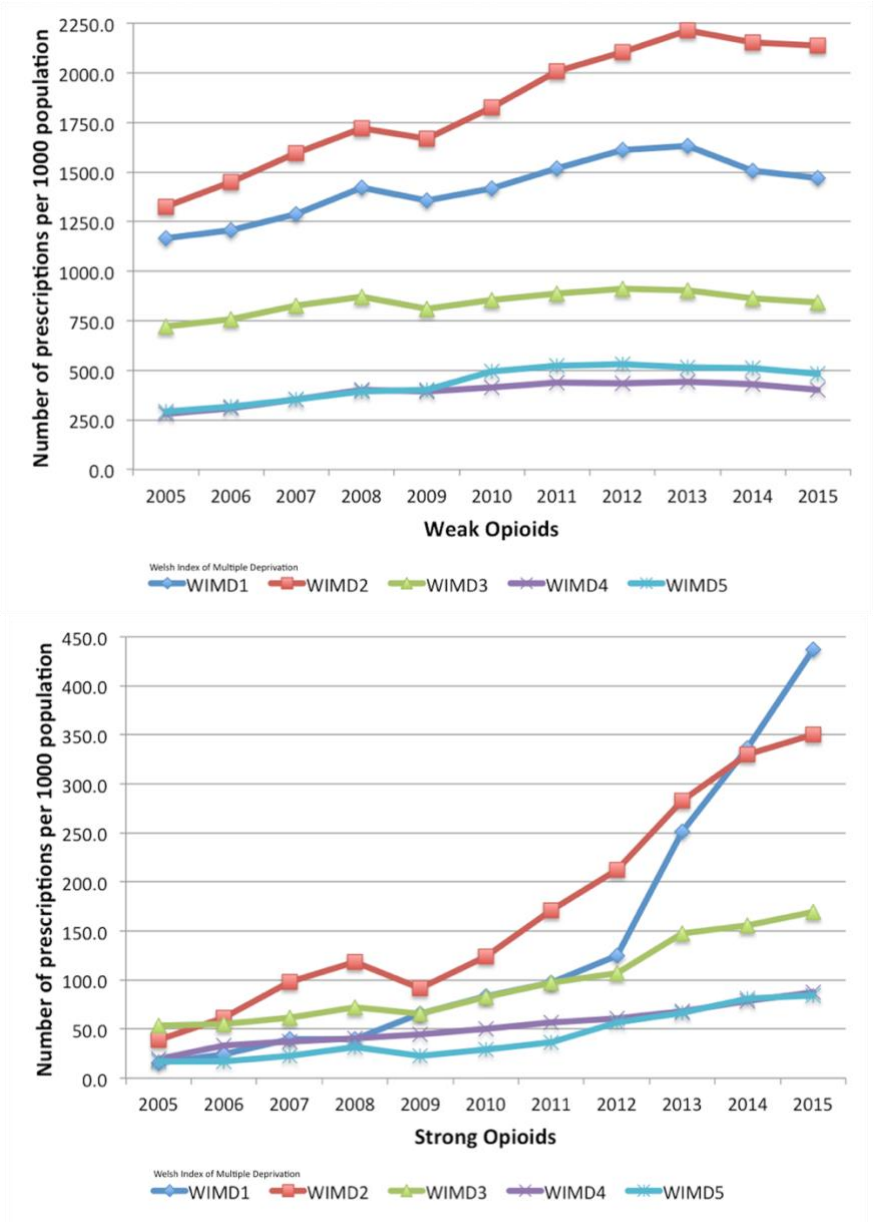


Figure I.31: Trends in the number of weak or strong opioid prescriptions issued per 1000 population in Powys Teaching Health Board by deprivation area (WIMD)
Welsh Index of Multiple Deprivation (WIMD) where WIMD1 = most deprived and WIMD5 = least deprived

Strong opioid prescribing increased 685% (from 143.7 to 1128.1 prescriptions per 1000 population) in Powys between 2005 and 2015. The most deprived areas of the Health Board had the least number of prescriptions issued in 2005 but rose significantly (2739.2%, from 15.4 to 437.2 prescriptions per 1000 population) over the study period. This was the largest increase in strong opioid prescription numbers seen anywhere in Wales in the time period examined. By 2015, there were 5 times more prescriptions being issued in the most deprived areas compared to the least deprived (Table I.50).

Appendix J Published papers, abstracts and presentations

2nd Prize, Royal Pharmaceutical Society Winter Conference, 2017

Trends in Strong Opioid Prescribing in a Primary Care Population

Preliminary results from the TOPAS Study

Emma Davies*#, Fatemeh Torabi**, Ashley Akbari**, Ceri Phillips*, Jaynie Rance*
*College of Human and Health Science, Swansea University, **Farr Institute, Swansea University Medical School

Introduction

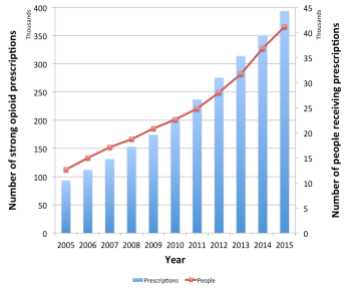
Previous studies have demonstrated dramatic increases in United Kingdom opioid prescribing over the last 20 years[1,2]. Given that up to 44% of the United Kingdom (UK) population have been estimated to live with pain[3] and there is little evidence to support the use of opioids in chronic non-cancer pain[4]; it is important to understand more about the people receiving these medicines. This is the first, large-scale observational study of opioid prescribing in Wales.

Method

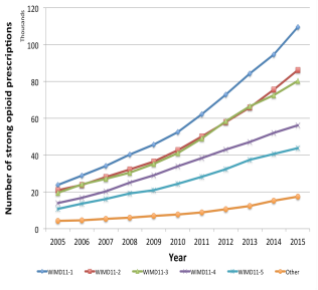
Data on all prescriptions for opioid containing medications issued between 2005 and 2015, were taken from the Secure Anonymised Information Linkage databank (SAIL). People with a diagnosis for cancer during the study period were excluded from the detailed analysis. Annual number of prescriptions, numbers of patients, age, gender, duration of prescribing, social deprivation and co-diagnosis of depression were measured in repeated cross-sections and analysed using descriptive statistics.

Results

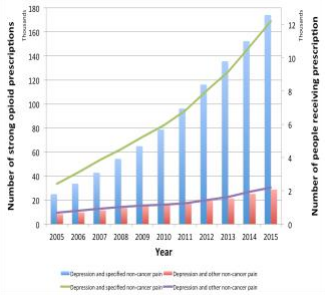
Between 2005 and 2015 there were 26,180,200 prescriptions for opioids issued to 1,223,503 people (55.9% female, 89.9% non-cancer) in the participating practices in Wales (78% of all practices). Strong opioid prescriptions for non-cancer pain increased by 323.4% (from 92,976 to 393,697) over the study period and comprised 11.5% of all opioid prescriptions.



Number of strong opioid prescriptions issued and people to whom prescriptions were issued each year 2005 - 2015



Number of strong opioid prescriptions issued by deprivation category (WIMD11-1 = most deprived, WIMD11-5 = least deprived)



Number of prescriptions and people receiving strong opioid prescriptions with concomitant depression diagnosis

There was a greater increase in opioid prescribing for females than males (233% compared to 184%). The areas with the highest level of deprivation (WIMD11-1) saw the greatest rise in strong opioid prescribing for non-cancer pain (380% over the study period). There was a 598.4% increase (from 24,933 to 174,134) in strong opioid prescriptions for people with co-diagnoses of either osteo- or rheumatoid arthritis, back or neck pain, fibromyalgia or neuropathic pain and depression.

Conclusion

There was an enormous rise in strong opioid prescribing in Wales between 2005 and 2015, in line with findings from other UK-based studies[1,2]. This is the first study of its type in the Principality and highlights some areas of concern, such as the link between strong opioid prescribing and depression. Whilst data quality is determined by the accuracy of the input at source; further analysis is planned to determine the significance of the results from a public health perspective and their clinical impact.

References

1. Zin, C. S., Chen, L. C. & Knaggs, R. D. *Eur J Pain* **18,** 1343–1351 (2014).
2. Ruscitto, A., Smith, B. H. & Guthrie, B. *Eur J Pain* **19,** 59–66 (2014)
3. Fayaz, A, P Croft, R M. Langford, L J. Donaldson, and G T. Jones. 2016. *BMJ open* 6(6):e010364
4. Chou, Roger, Jane C. Ballantyne, Gilbert J. Fanciullo, Perry G. Fine, and Christine Miaskowski. 2009. *J Pain* 10(2):147–59.

Acknowledgements

Research costs have been provided via a Galen Personal Award from Pharmacy Research UK

#PhD fellowship partly funded by Welsh Government through Health and Care Research Wales and the Research Capacity Building Collaboration programme

Pharmacy Research UK

#rcbcwales

@emma_davies50

Davies, E. et al. 2017. Abstract: Trends in strong opioid prescribing in a primary care population: preliminary results from the Trends in Opioid Prescribing and Associated Health Care Utilisation in Wales Study (TOPAS). *International Journal of Pharmacy Practice* 25(Suppl 2), p. 14. doi: 10.1111/ijpp.12417.

1st Prize College of Human and Health Sciences Post-Graduate Conference, September 2017

Trends in Opioid Prescribing by Deprivation in a Primary Care Population: Results from the TOPAS* Study

*Trends in Opioid Prescribing and Associated Resource Utilisation in Wales

Emma Davies
College of Human and Health Science, Swansea University

Introduction

It has been estimated that up to 48% of the population in the United Kingdom (UK) live with pain[1]. Pain prevalence has been shown to be higher in areas of greatest socio-economic deprivation[2]. This section of the TOPAS study examines trends in opioid prescribing by deprivation across Wales, between 2005 -2015.

Method

Data on all prescriptions for opioid containing medications issued between 2005 and 2015, were taken from the Secure Anonymised Information Linkage databank (SAIL). People with a diagnosis for cancer during the study period were excluded from the detailed analysis. Annual number of prescriptions, numbers of patients and social deprivation were measured in repeated cross-sections, adjusted for population and analysed using descriptive statistics.

Results

There were significantly more people receiving opioid prescriptions in the areas of Wales with highest levels of deprivation (WIMD1) (One-way ANOVA: WIMD1 mean 183.6, SD=11.1, WIMD5 mean 105.1, SD=8.2, $F(4,50)=109.6$, $p=.000$, $\eta^2=0.90$). There were 75% more people receiving weak opioids and 80% more people receiving strong opioids in the most deprived areas compared to the least deprived areas of the country.

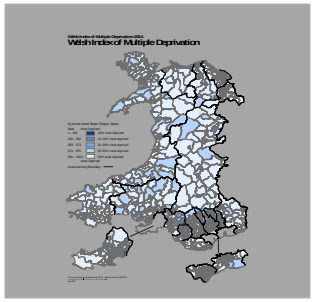
Nearly a third of all opioid prescriptions in Wales between 2005 and 2015, were issued in the most deprived areas. Those areas had a 347% increase in the annual number of strong opioid prescriptions and 140% more prescriptions issued than the least deprived areas of Wales. Weak opioid prescribing increased more in WIMD4 areas (lesser deprivation) although there were 140% more prescriptions issued in the areas of highest deprivation compared to the areas with least.

Conclusion

The substantial increase in opioid prescribing and the concentration of it, within areas of high deprivation have been noted in other UK-based studies. The reasons for greater pain prevalence and consequently, higher rates of opioid prescribing in areas of socio-economic deprivation are not well understood. Some authors have postulated that prescribing may be a substitute for timely access to good quality pain services.

Introduction

As much as 44% of the United Kingdom (UK) population have been estimated to live with pain[1] and prevalence has been shown to be higher in areas of greatest socioeconomic deprivation[2]. Although there is little evidence to support the use of opioids in chronic non-cancer pain[3], previous studies have demonstrated dramatic increases in opioid prescribing over the last 20 years in the United Kingdom[4,5]. This section of the TOPAS study examines the trends in opioid prescribing by deprivation across Wales between 2005 -2015, using data from the Secure Anonymised Information Linkage Databank (SAIL).

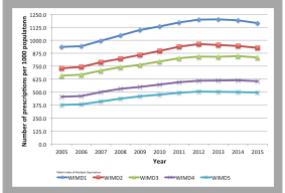


Method

Data on all prescriptions for opioid containing medications issued between 2005 and 2015, were taken from the Secure Anonymised Information Linkage databank (SAIL). Annual number of prescriptions, numbers of patients and deprivation (Welsh Index of Multiple Deprivation, WIMD) were measured in repeated cross-sections, adjusted for population and analysed using descriptive statistics.

SAIL

75% & 80% more people in WIMD1 areas received prescriptions for weak & strong opioids than in WIMD5 areas of Wales, respectively.



Annual trend in the number of opioid prescriptions per 1000 population in Wales by deprivation category. WIMD1 = most deprived, WIMD5 = least deprived

Results

29% of all prescriptions issued within WIMD1 areas

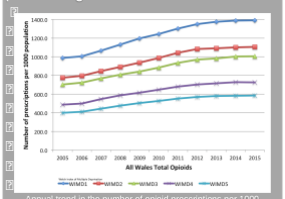
347% increase in the number of strong opioid prescriptions issued in WIMD1 areas

128% more strong opioid prescriptions issued in the WIMD1 compared to WIMD5 areas

Annual trend in the number of strong opioid prescriptions per 1000 population in Wales by deprivation category. WIMD1 = most deprived, WIMD5 = least deprived

140% more weak opioid prescriptions issued in WIMD1areas compared to WIMD5 areas

Largest increase (33%) in weak opioid prescribing was seen in WIMD4 areas



Annual trend in the number of opioid prescriptions per 1000 population in Wales by deprivation category. WIMD1 = most deprived, WIMD5 = least deprived

There was a substantial increase in opioid prescribing in all areas of Wales between 2005 and 2015. This is in line with findings from other UK-based studies[4,5].

Conclusion

The significant differences in prescribing between the most deprived and least deprived areas of the country have been noted by other authors[6] in the UK although the reasons for higher prevalence of pain and the consequent prescribing is not well understood.

There is postulation that prescribing acting as a proxy for poor access to quality pain services[7] and this may be especially relevant in more socio-economically deprived areas.

References

1. Fayaz, A, et al., 2016. *BMJopen*, 6(6):e010364
2. Health and Social Care Information Centre. Health survey for England 2011. Leeds: HSCIC, 2012.
3. Zin, C. S., Chen, L. C. & Knaggs, R. D. 2014. *Eur J Pain* **18**, 1343–1351.
4. Ruscitto, A., Smith, B. H. & Guthrie, B. 2014 *Eur J Pain* **18**, 59–68
5. Chou, R. et al., 2009. *J Pain* 10(2):147–59.
6. Mordecai, L. et al., 2015. *B J Gen Prac*, 68(668), pp e225–e233.
7. Finestone, H.M. et al., 2016. *Can Fam Phy*,62(6), pp.465–468.

Acknowledgements

Research costs have been provided via a Galen Personal Award from Pharmacy Research UK

Pharmacy Research UK

[a]PhD fellowship partly funded by Welsh Government through Health and Care Research Wales and the Research Capacity Building Collaboration programme

Original Article

British Journal of Pain
1–14

DOI: 10.1177/2049463718800737
journals.sagepub.com/home/bjp
SAGE

Examining patterns in opioid prescribing for non-cancer-related pain in Wales: preliminary data from a retrospective cross-sectional study using large datasets

Emma Davies[1], Ceri Phillips[1,2], Jaynie Rance[1] and Berni Sewell[2]

Abstract

Objectives: To examine trends in strong opioid prescribing in a primary care population in Wales and identify if factors such as age, deprivation and recorded diagnosis of depression or anxiety may have influenced any changes noted.

Design: Trend, cross-sectional and longitudinal analyses of routine data from the Primary Care General Practice database and accessed via the Secure Anonymised Information Linkage (SAIL) databank.

Setting: A total of 345 Primary Care practices in Wales.

Participants: Anonymised records of 1,223,503 people aged 18 or over, receiving at least one opioid prescription between 1 January 2005 and 31 December 2015 were analysed. People with a cancer diagnosis (10.1%) were excluded from the detailed analysis.

Results: During the study period, 26,180,200 opioid prescriptions were issued to 1,223,503 individuals (55.9% female, 89.9% non-cancer diagnoses). The greatest increase in annual prescribing was in the 18–24 age group (10,470%), from 0.08 to 8.3 prescriptions/1000 population, although the 85+ age group had the highest prescribing rates across the study period (from 149.9 to 288.5 prescriptions/1000 population). The number of people with recorded diagnoses of depression or anxiety and prescribed strong opioids increased from 1.2 to 5.1 people/1000 population (328%). The increase was 366.9% in areas of highest deprivation compared to 310.3 in the least. Areas of greatest deprivation had more than twice the rate of strong opioid prescribing than the least deprived areas of Wales.

Conclusion: The study highlights a large increase in strong opioid prescribing for non-cancer pain, in Wales between 2005 and 2015. Population groups of interest include the youngest and oldest adult age groups and people with depression or anxiety particularly if living in the most deprived communities. Based on this evidence, development of a Welsh national guidance on safe and rational prescribing of opioids in chronic pain would be advisable to prevent further escalation of these medicines.

Summary points

- This is the first large-scale, observational study of opioid prescribing in Wales.
- Over 1 million individual, anonymised medical records have been searched in order to develop the study cohort, thus reducing recall bias.
- Diagnosis and intervention coding in the Primary Care General Practice database is limited at input and may lead to under-reporting of diagnoses.

[1]College of Human and Health Sciences, Swansea University, Swansea, UK
[2]Swansea Centre for Health Economics, College of Human and Health Sciences, Swansea University, Swansea, UK

Corresponding author:
Emma Davies, College of Human and Health Sciences, Swansea University, Singleton Park, Swansea SA2 8PP, UK.
Email: 878970@swansea.ac.uk

Davies, E. et al. 2018. Examining patterns in opioid prescribing for non-cancer related pain in wales: preliminary data from a retrospective cross-sectional study using large datasets. *British Journal of Pain* 13(3), pp. 145–158. doi: 10.1177/2049463718800737.

1st Prize HSRRP Conference 2019, Birmingham University

Davies, E. 2019. Gender-based trends in opioid prescribing in a primary care population with recorded diagnoses of depression or anxiety; using a retrospective, cross-sectional analysis of a large dataset - Poster Abstracts. *International Journal of Pharmacy Practice* 27(Supplement_2), pp. 27–60. Available at: https://academic.oup.com/ijpp/article-pdf/27/Supplement_2/27/36130946/ijpp12533.pdf.

RCBC Conference May 2019

1st Prize College of Human and Health Sciences Post-Graduate Conference, June 2019

GENDER-BASED TRENDS IN OPIOID PRESCRIBING IN A PRIMARY CARE POPULATION WITH RECORDED DIAGNOSES OF DEPRESSION OR ANXIETY:

Using a retrospective, cross-sectional analysis of a large dataset

Emma Davies*, Berni Sewell**, Mari Jones**, Ceri Phillips*, Jaynie Rance*

* College of Human and Health Sciences, ** Swansea Centre for Health Economics

Background

50% Up to half the population of the United Kingdom (UK) live with persisting pain[1]

25% The World Health Organisation estimate that 1 in 4 adults have a mental health condition[2]

A higher prevalence of women than men with persistent pain has been previously reported in the literature[3]

Method

NHS read codes used to identify opioid prescriptions issued in Primary Care in Wales between 2005 and 2015, to people without a diagnosis of cancer

Read codes used to identify whether people had a recorded diagnosis of depression and/or anxiety

Number of prescriptions measured in repeated, annual cross-sections and adjusted to gender-population

Results

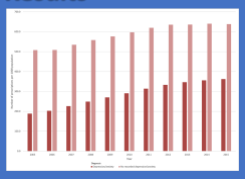


Figure 1: Trends in the annual number of opioid prescriptions issued and stratified by the presence of a recorded diagnosis of depression and/or anxiety (SAIL registered practices in Wales)

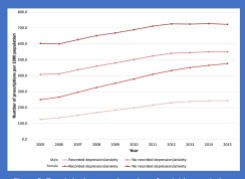


Figure 2: Trends in the annual number of opioid prescriptions issued and stratified by the presence of a recorded diagnosis of depression and/or anxiety and gender (SAIL registered practices in Wales)

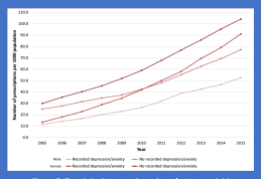


Figure 3: Trends in the annual number of strong opioid prescriptions issued and stratified by the presence of a recorded diagnosis of depression and/or anxiety and gender (SAIL registered practices in Wales)

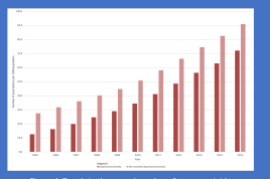


Figure 4: Trends in the annual number of strong opioid prescriptions issued and stratified by the presence of a recorded diagnosis of depression and/or anxiety (SAIL registered practices in Wales)

Results

32.7% of opioid prescriptions were issued to people with a diagnosis of depression and/or anxiety (RDDA)

41% of strong opioid prescriptions were issued to people with an RDDA

Twice as many prescriptions were issued to women (median 379.8 per 1000) as for men (median 198.4 per 1000) with an RDDA (U=.000, p=.000, r=0.8)

The annual number of strong opioid prescriptions for people with an RDDA increased by 474% in 11 years

Strong opioid prescriptions for women with an RDDA rose by 573% and for men by 356% over the study period

Discussion

- There have been substantial increases in opioid prescribing in Wales between 2005 and 2015. Greater percentage increases in the number of prescriptions were noted in people with an RDDA
- This study reinforces previous literature which describes higher prevalence of opioid prescribing in women. It is of concern that strong opioid prescribing has risen more quickly in women with an RDDA. Further research is needed to determine whether depression/anxiety are the cause or iatrogenic effect of increased opioid prescribing[4] and why women appear more susceptible

Acknowledgements

This work uses data provided by patients and collected by the NHS as part of their care and support

PhD funding supported by rcbcwales Pharmacy Research UK

References

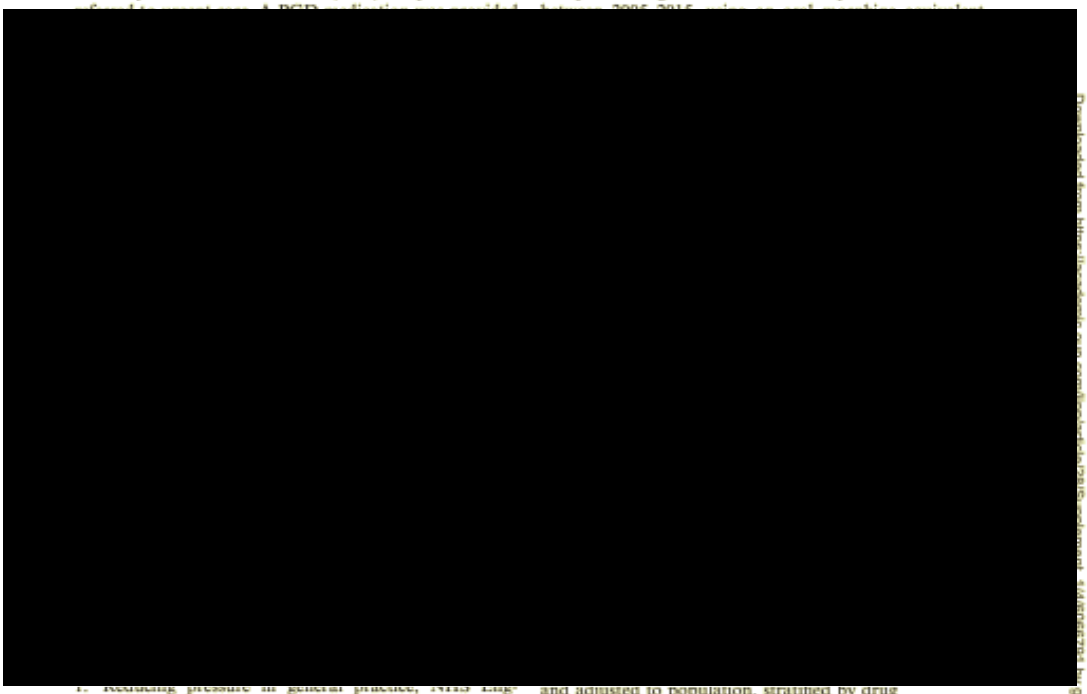
1. Fayaz, A. et al., 2016. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ open*, 6(6), p.e010364
2. World Health Report: Mental disorders affect 1 in 4 people. A product of NMH Communications. World Health Organization, Geneva, 2001. (https://www.who.int/whr/2001/media_centre/press_release/en/ accessed December 2018)
3. Tsang A, Korff Von M, Lee S, Alonso J, Karam E. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. 2008;9(10):883–91. Available from: http://www.sciencedirect.com/science/article/pii/S1526590008005750
4. Mazereeuw G, Sullivan MD, Juurlink DN. Depression in Chronic Pain: Might Opioids Be Responsible? Pain. 2018 Jun 13

consultation, using chi-squared tests. Any questionnaire free text comments were qualitatively explored for insight.

Results: In the first six months of the service, 741 patients were referred to one of the community pharmacies enrolled in the service ($n = 24$) to provide advice (15%), treatment with an over-the-counter product (47%) or same day referral back to the GP (14%). Six patients were

Introduction: Opioid prescribing has risen considerably in the UK over the last 20 years [1] and with it, comes increased risks to population health[2]. Opioid dose is an indicator of potential harm, but understanding the burden of different opioid medicines can be hampered by the numerous doses, strengths and products available.

Aims: The study aimed to describe trends in prescribing of opioid analgesics for non-cancer pain across Wales



land; https://www.england.nhs.uk/gp/gpfv/workload/releasing-pressure/ [Accessed online 11/04/2019].

Opioid Use

Examining trends in opioid prescribing burden using an oral morphine equivalence measure in a primary care population: a retrospective, cross-sectional study of primary care prescribing data

E. Davies, C. Phillips, B. Sewell, M. Jones and J. Rance

Swansea University, Swansea, UK

and adjusted to population, stratified by drug

	Total daily oral morphine equivalent dose (mg) prescribed			
Year	Codeine	Morphine	Tramadol	Total all opioids
2005	13743115	3293220	7865695	37662651
2015	25593382	17047800	14252335	76428768
Percentage change (%) 2005–2015	86.2	417.7	81.2	102.9
	Total daily oral morphine equivalent dose (mg) per 1000 population			
2005	5916	1422	3397	16266
2015	10581	7063	5905	31665
Rate change (%) 2005–2015	78.8	396.6	73.8	94.7
	Oral morphine equivalent dose per prescription issued (mg)			

Table 1. (Continued)

Year	Total daily oral morphine equivalent dose (mg) prescribed			
	Codeine	Morphine	Tramadol	Total all opioids
2005	17	86	36	23
2015	19	68	38	32
Percentage change (%) 2005–2015	16.2	−20.6	5.7	35.5

Conclusion: Large increases in OMED burden were

cally in many high-income countries in recent years.

Many of these deaths include those who inject illicit drugs, so may access NSP and people currently or recently in treatment for their addiction. Evidences suggest OST reduces both overdose and overall mortality but more needs to be done to prevent these deaths. UK guidance describes pharmacy practice to reduce overdose but the extent to which such guidance is implemented is questionable[1].

Aim: To describe CPs' self-reported adherence to guidelines for preventing overdose deaths.

Methods: A cross-sectional quantitative telephone survey was undertaken with CPs in England. A random stratified sampling technique was adapted to get representative sample from 6% of registered pharmacy pre-

pharmacies all needs attention. Nonparticipation of

Davies, E. et al. 2020. Examining trends in opioid prescribing burden using an oral morphine equivalence measure in a primary care population: a retrospective, cross- sectional study of primary care prescribing data. *International Journal of Pharmacy Practice* 28(S1), pp. 9–10. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/ijpp.12606.

BJGP Open

RESEARCH

Examining opioid prescribing trends for non-cancer pain using an estimated oral morphine equivalence measure: a retrospective cohort study between 2005 and 2015

Emma Davies[1,2]*, Bernadette Sewell[3], Mari Jones[4], Ceri J Phillips[5], Jaynie Y Rance[6]

[1]PhD Research Fellow, College of Human and Health Sciences, Swansea University, Swansea, UK; [2]Advanced Pharmacist Practitioner in Pain Management, Pharmacy and Medicines Management, Cwm Taf Morgannwg University Health Board, Abercynon, UK; [3]Senior Lecturer in Health Economics, Swansea Centre for Health Economics, Swansea University, Swansea, UK; [4]Research Officer, Swansea Centre for Health Economics, Swansea University, Swansea, UK; [5]Professor of Health Economics, College of Human and Health Sciences, Swansea University, Swansea, UK; [6]Professor of Public Health, Policy and Social Sciences, College of Human and Health Sciences, Swansea University, Swansea, UK

Abstract

Background: Over the past 20 years prescription of opioid medicines has markedly increased in the UK, despite a lack of supporting evidence for use in commonly occurring, painful conditions. Prescribing is often monitored by counting numbers of prescriptions dispensed, but this may not provide an accurate picture of clinical practice.

Aim: To use an estimated oral morphine equivalent ($OMEQ_e$) dose to describe trends in opioid prescribing in non-cancer pain, and explore if opioid burden differed by deprivation status.

Design & setting: A retrospective cohort study using cross-sectional and longitudinal trend analyses of opioid prescribing data from Welsh Primary Care General Practices (PCGP) took place. Data were used from the Secure Anonymised Information Linkage (SAIL) databank.

Method: An $OMEQ_e$ measure was developed and used to describe trends in opioid burden over the study period. $OMEQ_e$ burden was stratified by eight drug groups, which was based on usage and deprivation.

Results: An estimated 643 436 843 milligrams (mg) $OMEQ_e$ was issued during the study. Annual number of prescriptions increased 44% between 2005 and 2015, while total daily $OMEQ_e$ per 1000 population increased by 95%. The most deprived areas of Wales had 100 711 696 mg more $OMEQ_e$ prescribed than the least deprived over the study period.

Conclusion: Over the study period, $OMEQ_e$ burden nearly doubled, with disproportionate $OMEQ_e$ prescribed in the most deprived communities. Using $OMEQ_e$ provides an alternative measure of prescribing and allows easier comparison of the contribution different drugs make to the overall opioid burden.

***For correspondence:** 878970@swansea.ac.uk

Competing interest: The authors declare that no competing interests exist.

Received: 19 May 2020
Accepted: 22 June 2020
Published: 02 December 2020

Author Keywords: primary health care, social deprivation, cohort studies, opioid prescribing, analgestics, opioid

DOI:10.3399/bjgpopen20X101122

Davies, E. et al. 2020. Examining opioid prescribing trends for non-cancer pain using an estimated oral morphine equivalence measure: a retrospective cohort study between 2005 and 2015. *BJGP Open* 17(8), p. bjgpopen20X101122-13. Available at: http://bjgpopen.org/lookup/doi/10.3399/bjgpopen20X101122.

Original Manuscript

THE BRITISH PAIN SOCIETY
EXPERTISE WHERE IT MATTERS

Healthcare resource utilisation and cost analysis associated with opioid analgesic use for non-cancer pain: A case-control, retrospective study between 2005 and 2015

British Journal of Pain
2021, Vol. 0(0) 1–14


Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/20494637211045898
journals.sagepub.com/home/bjp
SAGE

Emma Davies[1], Ceri J Phillips[1], Mari Jones[2] and Bernadette Sewell[1]

Abstract

Objective: To examine differences in healthcare utilisation and costs associated with opioid prescriptions for non-cancer pain issued in primary care.

Method: A longitudinal, case-control study retrospectively examined Welsh healthcare data for the period 1 January 2005–31 December 2015. Data were extracted from the Secure Anonymised Information Linkage (SAIL) databank. Subjects, aged 18 years and over, were included if their primary care record contained at least one of six overarching pain diagnoses during the study period. Subjects were excluded if their record also contained a cancer diagnosis in that time or the year prior to the study period. Case subjects also received at least one prescription for an opioid analgesic. Controls were matched by gender, age, pain-diagnosis and socioeconomic deprivation. Healthcare use included primary care visits, emergency department (ED) and outpatient (OPD) attendances, inpatient (IP) admissions and length of stay. Cost analysis for healthcare utilisation used nationally derived unit costs for 2015. Differences between case and control subjects for resource use and costs were analysed and further stratified by gender, prescribing persistence (PP) and deprivation.

Results: Data from 3,286,215 individuals were examined with 657,243 receiving opioids. Case subjects averaged 5 times more primary care visits, 2.8 times more OPD attendances, 3 times more ED visits and twice as many IN admissions as controls. Prescription persistence over 6 months and greater deprivation were associated with significantly greater utilisation of healthcare resources. Opioid prescribing was associated with 69% greater average healthcare costs than in control subjects. National Health Service (NHS) healthcare service costs for people with common, pain-associated diagnoses, receiving opioid analgesics were estimated to be £0.9billion per year between 2005 and 2015.

Conclusion: Receipt of opioid prescriptions was associated with significantly greater healthcare utilisation and accompanying costs in all sectors. Extended prescribing durations are particularly important to address and should be considered at the point of initiation.

Keywords
Opioid analgesics, non-cancer pain, resource utilisation, healthcare costs, cost analysis

How this fits in

It is known that opioid analgesics can have long-term, harmful effects other than misuse and dependence. Previous studies examined the association between healthcare utilisation and the presence of opioid-induced adverse effects or misuse. This study examined the relationship between opioid prescribing for a range of pain-

[1]College of Human and Health Sciences, Swansea University, Swansea, UK
[2]Swansea Centre for Health Economics, Swansea University College of Human and Health Sciences, Swansea, UK

Corresponding author:
Emma Davies, College of Human and Health Sciences, Swansea University, Singleton Park, Sketty Lane, Swansea, Wales, SA2 8PP, UK.
Email: esdavies500@gmail.com

Davies E. et al. 2021 Healthcare resource utilisation and cost analysis associated with opioid analgesic use for non-cancer pain: A case-control, retrospective study between 2005 and 2015. *Br J Pain* 204946372110458 (2021) doi:10.1177/20494637211045898.