MONASH University

Evaluation of opioid analgesic use: patterns, predictors and outcomes

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Abstract

Opioid analgesics play an integral role in pain management. Improved quality of life and improved functional capacity are considered to be key outcomes of chronic non-cancer pain (CNCP) management. Yet, evidence suggests that opioid treatment of CNCP, the most common indication for prescription opioid analgesics, does not fulfil these key outcomes. Population-level increases in opioid-related harm also suggest that prescription opioid analgesics may not always be prescribed, dispensed or used in accordance with the best available evidence.

The overall objective of this thesis was to examine the patterns, predictors and outcomes associated with the use of prescription opioid analgesics. Firstly, a scoping review exploring harms and documented risk factors associated with extramedical prescription opioid analgesic use in Australia was undertaken. The review highlighted that extramedical prescription opioid analgesic use is associated with a range of harms, including fatal and non-fatal overdose. Polysubstance use with other centrally-acting substances is often implicated.

Three studies were then performed that investigated the use of prescription opioid analgesics utilising data from a random 10% sample of people who accessed medicines through Australia's Pharmaceutical Benefits Scheme. Rates of prescription opioid analgesic use were found to have remained high in Australia since 2013, with approximately 3 million adults using opioids and over 1.9 million adults initiating opioids each year. Between 2013 and 2017, the prevalence of opioid use increased slightly but incidence decreased. Initiation of strong opioids increased over time, reinforcing concerns about increased use and the harms associated with strong opioids in the community. In total, 2.6% of adults initiating opioids for non-cancer pain become persistent opioid-users over a 12-month period. Patient-specific characteristics (older age, prior history of mental health comorbidities and use of non-opioid analgesics) and prescriber choice of initial opioid were found to strongly predict persistent use. Among people who initiate weak opioids, 7.3% transitioned to strong opioids over 12-months.

Additionally, 1.4% of people who initiated opioids escalated to doses ≥50 mg oral morphine equivalents (OMEs) per day and 0.8% escalated to doses ≥90 mg OMEs per day over a 12-month period. People with cancer, men and people aged ≥75 years transitioned more rapidly to strong and high-dose opioids. The results from all three studies describing patterns of opioid use in Australia have clinical practice and policy implications because long-term, high-dose and high-potency opioid use have been associated with substantial morbidity and mortality. Overall these findings highlight several high-risk prescribing practices/utilisation patterns that may be markers for potential harm particularly among people with CNCP.

CNCP is a leading cause of disability often measured by sickness absence (SA) and disability pension (DP) days among working-age people. It was not possible to investigate the association between opioid initiation and SA/DP in the Australian population. Using linked data from Swedish national registries, the trajectories of SA/DP before and after strong and weak opioid initiation for non-cancer pain and the factors associated with these trajectories were identified. Three-quarters of people initiating opioids for non-cancer pain had persistent low/minimum levels of SA/DP 5-years before and after initiation. Patterns of SA/DP appeared to reflect a continuation of pre-initiation patterns among all trajectories. Although the possibility that opioids benefit specific patients cannot be excluded, at a population level, opioid initiation did not seem to be associated with a change in the pattern of SA/DP.

The results from this thesis have contributed to addressing several research gaps related to opioid use. Complex patterns of opioid use on an individual and population level identified suggest that large coordinated infrastructures and champions at the national, state and local levels are required to address opioid-related harm in Australia. Patient-centred, multifaceted strategies, with clearly defined and agreed upon expectations and goals of pain management, are crucial for safe opioid prescribing and use.

Publications during enrolment

Journal publications in thesis (thesis chapter order):

1. **Lalic S**, Jokanovic N, Ilomäki J, Gisev N, Lloyd B, Lubman DI, Bell JS. Harms associated with extramedical use of prescription opioid analgesics in Australia: A scoping review: Res Social Adm Pharm. 2019; 15(8):925-935.

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3. **Lalic S**, Gisev N, Bell JS, Korhonen MJ, Ilomäki J. Predictors of persistent prescription opioid analgesic use among people without cancer in Australia. Br J Clin Pharmacol. 2018;84(6):1267-1278.

4. **Lalic S**, Gisev N, Bell JS, Ilomäki J. Transition to high-dose or strong opioids: a population-based study of people initiating opioids in Australia. Addiction. 2019; *revised October.*

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Other peer-reviewed articles published during my PhD candidature

1. **Lalic S**, Wimmer BC, Tan EC, et al. Satisfaction with care and health-related quality of life among residents of long-term care facilities. J Am Med Dir Assoc. 2016;17(2):180-2

2. **Lalic S**, Sluggett JK, Ilomaki J, et al. Polypharmacy and medication regimen complexity as risk factors for hospitalization among residents of long-term care facilities: A prospective cohort study. J Am Med Dir Assoc. 2016;17(11):1067.e1-.e6

3. **Lalic S**, Jamsen KM, Wimmer BC, et al. Polypharmacy and medication regimen complexity as factors associated with staff informant rated quality of life in residents of aged care facilities: a cross-sectional study. Eur J Clin Pharmacol. 2016;72(9):1117-24

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All conference presentations occurring during my PhD candidature

1. Negative outcomes associated with extramedical use of prescription opioid analgesics in Australia: a scoping review. ASCEPT. Melbourne, Victoria (27 Nov-30 Nov 2016). Poster

2. Predictors of persistent use of prescription opioid analgesics among people without cancer. ACPE. Brisbane, Queensland (29 Oct-31 Oct 2017). Oral

3. Negative outcomes associated with extramedical use of prescription opioid analgesics in Australia: a scoping review. ACPE. Brisbane, Queensland (29 Oct-31 Oct 2017). Poster

4. What are the predictors of persistent prescription opioid analgesic use for non-cancer pain in Australia? APSA-ASCEPT. Brisbane, Queensland (5 Dec-8 Dec 2017). Oral and poster
   - Awarded the Pharmacoepidemiology SIG Prize

5. Predictors of Persistent Prescription Opioid Analgesic Use Among People Without Cancer in Australia: a Retrospective Cohort Study. ISPE. Prague, Czech Republic (22 Aug-25 Aug 2018). Oral

6. Prevalence and incidence of prescription opioid analgesic use in Australia. SHPA. Brisbane, Queensland (22 Nov- 25 Nov 2018). Poster

7. Trajectories of work disability before and after opioid initiation for non-cancer pain: 10-year population-based study. ASCEPT. Adelaide, South Australia (27 Nov- 30 Nov 2018). Poster

8. Prevalence and incidence of prescription opioid analgesic use in Australia. ASCEPT. Adelaide, South Australia (27 Nov- 30 Nov 2018). Oral and poster

9. Identifying patients at high risk of opioid-related harm in a busy tertiary hospital: where do we start? Choosing Wisely Australia National Meeting 2019, Victoria (May 2019). Poster

10. Transition to high-dose or strong opioids: A population-based study of people initiating opioids in Australia. ACPE. Japan (11 Oct – 13 Oct 2019). Oral

- Awarded the Rising Star Award

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals and one submitted publication. The core theme of the thesis is the evaluation of opioid analgesic use. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, Samanta Lalic, working within the Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences under the supervision of Prof J Simon Bell, Dr Jenni Ilomäki and Dr Natasa Gisev.

(The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.)

In the case of Chapters Two, Three, Four, Five and Six, my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status**	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student**
2	Harms associated with extramedical use of prescription opioid analgesics in Australia: a scoping review	In press	65%: Concept and design of study, literature search, screening of articles, data extraction, quality assessment, writing first draft and finalising manuscript	**N. Jokanovic:** Concept and design of study, screening of articles, data extraction, quality assessment, review of manuscript (10%) **J. Ilomäki:** Concept and design of study, review of manuscript (5%) **N. Gisev:** Concept and design of study, review of manuscript (5%) **B. Lloyd:** Concept and design of study, review of manuscript (5%) **D.I. Lubman:** Concept and design of study, review of manuscript (5%) **J.S. Bell:** Concept and design of study, review of manuscript (5%)	Yes No No No No No
3	Prevalence and incidence of	Published	65%: Concept and design of study, data	**J. Ilomäki:** Concept and design of study, review of manuscript (10%) **J.S. Bell:** Concept and design of study, review of manuscript (10%)	No No

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student
	prescription opioid analgesic use in Australia		analysis, writing first draft and finalising manuscript	**M.J. Korhonen:** Concept and design of study, review of manuscript (5%) **N. Gisev:** Concept and design of study, review of manuscript (10%)	No No
4	Predictors of persistent prescription opioid analgesic use among people without cancer in Australia	Published	65%: Concept and design of study, data analysis, writing first draft and finalising manuscript	**N. Gisev:** Concept and design of study, review of manuscript (10%) **J.S. Bell:** Concept and design of study, review of manuscript (10%) **M.J. Korhonen:** Concept and design of study, review of manuscript (5%) **J. Ilomäki:** Concept and design of study, review of manuscript (10%)	No No No No
5	Opioid escalation in Australia: a national population-based study	Revision submitted	70%: Concept and design of study, data analysis, writing first draft and finalising manuscript	**N. Gisev:** Concept and design of study, review of manuscript (10%) **J.S. Bell:** Concept and design of study, review of manuscript (10%) **J. Ilomäki:** Concept and design of study, review of manuscript (10%)	No No No
6	Trajectories of sickness absence	Published	50%: Concept and design of study, data	**J.S Bell:** Concept and design of study, review of manuscript (10%) **H. Gyllensten:** Concept and design of study, review of manuscript (5%)	No No

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student
	and disability pension before and after opioid initiation for non-cancer pain: 10-year population-based study		analysis, writing first draft and finalising manuscript	**N. Gisev:** Concept and design of study, review of manuscript (5%) **E. Friberg:** Concept and design of study, review of manuscript (5%) **J. Ilomaki:** Concept and design of study, review of manuscript (5%) **J.K. Sluggett:** Concept and design of study, review of manuscript (5%) **E. Mittendorfer-Rutz:** Concept and design of study, review of manuscript (5%) **K. Alexanderson:** Concept and design of study, review of manuscript (10%)	No No No No No No

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: S. Lalic **Date:** 30/6/19

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: S. Bell **Date:** 30/6/19

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CDC Centers for Disease Control and Prevention

CI Confidence interval

CNCP Chronic non-cancer pain

CNS Central nervous system

COX1 Cyclo-oxygenase-1

COX2 Cyclo-oxygenase-2

DDD Defined daily dose

DP Disability pension

DSM-5 Diagnostic and Statistical Manual of Mental Disorders, 5th edition

ED Emergency Department

GI Gastrointestinal

GDP Gross domestic product

IASP International Association for the Study of Pain

INCB International Narcotics Control Board

MHR My Health Record

NMP National Medicines Policy

NSAIDs Non-steroidal anti-inflammatory drugs

OIH Opioid induced hyperalgesia

OME Oral morphine equivalent

OUD Opioid use disorder

PBS Pharmaceutical Benefits Scheme

PDMP Prescription Drug Monitoring Programs

PHRN Population Health Research Network

PSP Prescription Shopping Program

QUM Quality use of medicines

RCT Randomised Controlled Trial

RR Risk Ratio

SA Sickness absence

s-DDD Defined daily doses for statistical purposes

US United States

WHO World Health Organization

YLDs Years Lived with Disability

Chapter One – Background

As a clinical pharmacist working in the Emergency Department (ED) at a tertiary teaching hospital, I started seeing an increasing number of patients presenting to ED after an accidental opioid overdose. I was also being asked to dispense an increased number of prescriptions for strong opioids. These prescriptions did not always appear to be the most appropriate choice for the patient or match their intensity or likely duration of pain, or were not consistent with the limited evidence that existed for the condition being treated. Moreover, the prescriptions I was receiving were for large quantities of opioids prescribed for conditions that only required at most 1-2 days of treatment. At this time, the opioid crisis in the United States (US) was being widely reported in the professional and lay media. The crisis in the US, in addition to the trends I was starting to see at just one hospital, made me ponder about the Australian opioid situation. Were we facing the same issues as the US? What led to the crisis in the US and what role did health practitioners play in this 21st century epidemic? I was interested to know whether certain prescribing patterns conferred a greater risk of dependence, overdose and other adverse events. These were all the reasons that directed me to undertake this thesis evaluating the patterns, predictors and outcomes of prescription opioid analgesic use.

I started my research seeking to better understand opioid prescribing patterns in Australia and what the corresponding outcomes of these patterns of use were. I conducted a scoping review to identify extramedical opioid use and the risk factors and harms associated with this type of use. To my surprise, many cases of accidental overdose death investigated by the coroner were among people who initiated on opioids for chronic non-cancer pain (CNCP). This finding in combination with my clinical findings, were the basis for my desire to understand how the prescribing and dispensing patterns of opioids could lead to these adverse events. I came to the conclusion that the 10% random sample of the Pharmaceutical Benefits Scheme (PBS) data provided an under-utlised data source for investigating these patterns in Australia. This data source could provide an opportunity to investigate population and individual level patterns and

predictors of opioid use in Australia. The PBS data source is considered large and nationally representative of the medicine dispensing patterns in Australia and therefore suited my research requirements well. Through the use of various methods (which will be discussed further throughout this thesis), the PBS data provided answers to most of the questions that I had. However, the PBS data were not linked to other data and therefore only captured medicine dispensings. This meant that it was not possible to investigate all outcomes identified as important indicators of opioid effect for the management of CNCP. These outcomes, as identified by the International Association for the Study of Pain (IASP), include functional and work capacity and are considered important socioeconomic factors among people with CNCP. A study investigating opioid use and work disability was not possible in Australia due to the lack of population level data on work disability. Therefore, it was necessary to collaborate with international colleagues to address this question. To ensure that the findings could have implications for Australia, this collaboration needed to be with a country that had a similar health care system and access to opioids. Additionally, the country needed to have population-level data on work disability that could be linked to dispensing data. Sweden suited these needs well. Hence, a collaboration was established with the Division of Insurance Medicine at Karolinska Institutet to conduct this important outcome-based study.

The overall aim of this thesis was to evaluate the patterns, predictors and outcomes of prescription opioid analgesic use. The studies in this thesis analysed general populations from Australia and Sweden who used prescription opioid analgesics. This was considered to be an essential component of this thesis in order to gain a comprehensive understanding of the patterns, predictors and outcomes associated with opioid use. The key similarities between the two studied populations are that Australia and Sweden both have universal health-care systems with similar access to opioids.

1.1 Introduction

Opioid analgesics play an integral role in pain management. The term 'opioid' refers to natural, semi-synthetic and synthetic drugs derived from or based on opium.[1] Opium is extracted from the poppy plant Papaver somniferum.[2, 3] Opium use dates back to around 3400 BC.[4] In 1806, morphine was isolated, extracted and named after the Greek god "Morpheus".[4] This resulted in increased morphine use worldwide.[3] In the years that followed, interest in opioid synthesis resulted in manufacture of various opioid analgesics.[5] Due to high rates of dependence at the end of the 19th century and beginning of the 20th century,[6] medical use of opioids was restricted to use in cancer pain. During the second half of the 20th century, opioids were also used short-term for severe acute pain,[6] but concern over dependence from long-term use limited their use for chronic non-cancer pain (CNCP).[7] In 1986, Portenoy and Foley[8] published the first report on the safety and efficacy of long-term opioids prescribed to 38 patients with CNCP. This was followed by other small studies confirming Portenoy and Foley's findings.[9, 10] In 1990, a seminal article entitled "The Tragedy of Needless Pain"[11] was published that advocated that "morphine taken solely to control pain is not addictive. Yet patients worldwide continue to be undertreated and to suffer unnecessary agony". Concurrently, there was increased recognition of the societal burden of chronic pain and concerns about the under-treatment of pain. Pain specialists and advocacy organisations began to argue that the US faced an epidemic of untreated pain.[12] Campaigns including pain as the 'the fifth vital sign' were initiated to raise awareness among health professionals on pain assessment and management.[12] These initiatives advocated a change in perspective around the use of opioids for CNCP.[12] Coinciding with this shift was the introduction, marketing and promotion of long-acting opioids, in particular oxycodone controlled release, for the treatment of non-cancer pain.[13] Almost three decades ago, these collective events resulted in widespread use of opioids for CNCP.

Expanding the indication for opioid use, among other factors, has led to a doubling in opioid use worldwide between 2001– 2003 and 2011–2013.[14-17] This increase is mainly attributed to an increase in opioid use in the developed countries, while use remains low in most parts of Africa,

Asia, Central America, the Caribbean, South America, and eastern and southeastern Europe.[18] Increasing opioid use has been associated with parallel increases in opioid-related mortality and morbidity, including dependence, hospitalisations and overdose.[1, 19-22] The connection between opioids and these harms were recognised at a population level towards the end of the first decade of the 2000s.[23, 24] Evidence of harms has since re-challenged the use of opioids for CNCP. While the effectiveness of opioids has been established for acute[2] and cancer[25] pain, the long-term effectiveness in CNCP is uncertain.[26] High-risk prescribing patterns of opioids have been identified and continue to be a concern. Guidelines for opioid prescribing in CNCP have been developed to assist clinicians with managing this complex condition and reducing the risk of harm.[27-29] A nuanced approach toward opioid prescribing that acknowledges both their potential for benefit and their risks is necessary.

This first chapter provides an overview of the burden of pain including work related outcomes and the challenges related to the use of opioids. The primary focus will be on the issues surrounding opioid use among people with CNCP, exploring the similarities and differences among various countries including Australia, Europe (with a primary focus on Sweden), US and Canada.

1.2 Pain

Pain is defined as an unpleasant sensory and emotional experience which may be an indicator of actual or potential tissue damage,[30] but may also be experienced in the absence of an identifiable cause.[30] Pain is a subjective and an individual, multifactorial experience influenced, by attitudes, beliefs, culture, previous pain experience expectations, mood and ability to cope.[30] There are three main categories of pain: acute, chronic and cancer pain. Acute pain usually lasts for a short time and occurs following trauma, surgery or other conditions.[31] Chronic pain is a highly complex condition that lasts beyond the time expected for healing following trauma, surgery or other conditions and may not have a clear reason for the pain.[31] Chronic pain has been operationally defined as persistent or recurrent pain lasting longer than three months.[32, 33] Cancer pain can occur in patients at all stages of cancer, however it is more common with advanced disease.[34]

Severe and debilitating pain due to side effects of treatment can also be a cause of cancer pain in cancer survivors.[34]

Traditionally pain was also categorised as nociceptive and neuropathic pain.[30, 35] However, it was later realised that people may have a combination of nociceptive and neuropathic pain which has been referred to as mixed pain.[36] Activity in neural pathways secondary to actual tissue damage or potentially tissue-damaging stimuli can result in nociceptive pain.[35] Neuropathic pain can result from a disease, lesion or dysfunction of the nervous system.[35] Neuropathic pain may be present without any readily demonstrable physical findings.[35] Recently, the term 'nociplastic pain' has been introduced by the IASP.[30] Nociplastic pain is defined as '*Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain*'.[30] These categorisations and definitions begin to demonstrate the complexities associated with pain diagnosis and management. Pain conditions often need to be managed using a multimodal and multidisciplinary approach. Multimodal treatment involves the concurrent use of various therapeutic interventions including non-pharmacological and pharmacological therapeutic options. It has become recognised that interventions should have different mechanisms of action aimed at different pain mechanisms.[30]

1.2.1 Acute pain

Acute pain usually lasts for a short time (ranging from seconds to <3 months) and typically occurs following trauma, surgery or other conditions. The prevalence of acute pain in the general population is difficult to determine. Acute pain is a common symptom across all hospital settings, with prevalence rates ranging from 37-84% among hospital patients.[37] Acute pain can transition into chronic pain.[38-40] The mechanisms of this transition are complex involving biological, psychosocial and socioenvironmental factors.[38, 39] The incidence of the transition from acute post-surgical pain to chronic post-surgical pain ranges from 2% to 85% depending on the type of surgery, location of pain and the definition used for chronic pain.[38, 41] The primary goal of acute

pain management is to provide treatment that reduces pain intensity, while allowing individuals to maintain function and quality of life.[40] Increasingly it has been recognised that it is important to prevent the transition of acute pain to chronic pain.[42] This includes effectively managing early postsurgical pain with a combination of analgesics including opioids. However, further studies are required to determine the most effective preventative strategies to reduce the risk of transitioning to chronic pain.[42]

1.2.2 Chronic pain

Chronic pain is a highly complex condition that lasts beyond the time expected for healing following trauma, surgery or other conditions and may not have a clear reason for the pain.[43] CNCP is a major public health issue worldwide.[44] CNCP interferes with daily activities, physical and mental health, family and social relationships, and interactions in the workplace.[45] CNCP is a leading cause of disability worldwide (Table 1),[46] and is a large constituent of health expenditure in many middle and high income countries, mostly due to indirect costs including sickness absence (SA) and disability pension (DP).[47-50] The published prevalence rates of CNCP range worldwide from 7% to over 60% depending on the definition used.[33, 51-54] While pain affects all populations, regardless of age, sex, income, race/ethnicity, or geography, it is not distributed equally across the globe.[44] CNCP prevalence rates appear to be similar in Australia and Sweden, although differing definitions for CNCP are often used in studies in each country. CNCP was reported by 17.1% of males and 20.0% of females in a survey of a random sample of the Australian population, defined as pain experienced every day for three months in the six months prior to interview.[52] According to a large scale computer-assisted telephone survey, the estimate for CNCP in Sweden is 18%. CNCP in this study was defined as pain lasting more than 6 months, having pain during the last month, several times during the last week, and last experienced pain having an intensity 5 or more on a Numeric Rating Scale: 1 (no pain) to 10 (worst pain imaginable).[53] The estimate for CNCP in Sweden and Australia were similar to the overall prevalence of CNCP in Europe (19%), based on the same study.[53] The terms chronic pain, chronic non-cancer pain and CNCP will be used interchangeably in this thesis.

Table 1. Top 10 causes of global years lived with disability (YLDs) in 2013 adapted from the Global Burden of Disease study.[46]

Condition	Mean YLDs[1] ('000)
Low back pain	**72,318**
Major depression	51,784
Iron-deficiency anaemia	36,663
Neck pain	**34,348**
Other hearing loss	32,580
Migraine	**28,898**
Diabetes	29,518
COPD	26,131
Anxiety disorders	24,356
Other musculoskeletal disorders	**22,644**

Bolded text represents CNCP conditions.

[1]YLDs was equal to the sum of prevalence of the condition multiplied by the general public's assessment of the severity of health loss.

There are many processes that contribute to chronic pain including inflammatory, neuropathic, central and physiological.[55] Common chronic pain conditions include: chronic headache or migraine, painful diabetic peripheral neuropathy, painful postherpetic neuralgia, fibromyalgia, osteoarthritis, rheumatoid arthritis, back and neck pain, and other musculoskeletal conditions. Four of the top 10 global causes of YLDs were CNCP conditions (Table 1). Recently it has been argued that CNCP needs to be considered a disease itself, rather than the paradigmatic view of pain being a symptom of disease.[44] This thesis will primarily focus on opioid use in CNCP.

1.2.3 Cancer pain

Pain associated with cancer is termed cancer pain. Cancer pain can occur in patients with early stage and advanced disease and also as a severe and debilitating side-effect of treatment in cancer survivors.[34] Approximately one-third of adults who are actively receiving treatment for cancer and two-thirds of those with advanced malignant disease experience pain.[34] A systematic review pooled data from 52 studies and found the prevalence of pain was >50% in all cancer types, with the highest prevalence in head/neck cancer patients.[56] The World Health Organization (WHO) developed a 3-step analgesic ladder for the treatment of cancer pain starting with the use of non-opioid analgesics.[22, 25, 57, 58] This analgesic ladder approach is widely accepted as the basis for cancer treatment guidelines.[25, 57] However, there are suggestions to either eliminate the second step of the analgesic ladder or replace it with low dose opioids rather than weak opioids.[1] In addition to the WHO guidelines, the European Society for Medical Oncology and the European Association for Palliative Care recommend that opioids should be used for the management of cancer pain.[25, 57] The guidelines suggest that cancer pain, particularly among patients with advanced or metastatic disease, be managed from the holistic perspective of palliative care.[25, 59, 60] This aims to maintain quality of life throughout the course of disease and manage the challenges that can occur as patients approach the end of life.[25, 59, 60]

1.3 Management of CNCP

The management of CNCP, as with other non-communicable diseases, has changed over time including using opioids to manage CNCP. Clinical guidelines have been developed to guide the various types and categories of pain. In general terms, multimodal and multidisciplinary management approaches are recommended for all types of pain. The recent guidelines for opioid prescribing in CNCP have reinforced this aspect of management.[27-29] To date, there have been no evaluations of outcomes (e.g. overdose deaths) associated with opioid guideline implementation.[61] However, the release of opioid guidelines in the ED in Ohio was associated with a decrease in quantity of opioid prescriptions.[62] Additionally, Bohnert et al[63] investigated whether the release of the Centers for Disease Control and Prevention (CDC) guideline

corresponded to declines in specific opioid prescribing practices. They found that several opioid prescribing practices were decreasing before the CDC guideline, however, there was a greater decline at the time of its release.[63] It was unclear whether this translated to a reduction in harm from this study, but it suggested that clinical guidelines were at least partly effective in changing prescribing practice.[63]

Traditionally, the management of CNCP has been mainly focused on pain intensity. Analgesics, a class of medicines affecting different pain pathways, are available to manage pain. These include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids. There are also other adjuvant agents including antidepressants, antiepileptics, local anaesthetics, clonidine and ketamine which are used for pain management. WHO's analgesic ladder initially developed for cancer pain has been extrapolated for use in acute and CNCP. According to this ladder, analgesics are used in a step-wise approach based on pain intensity. It is recommended that analgesics are used in combination with non-pharmacological therapies including cognitive behavioural therapy, exercise and physiotherapy.

Recently, the notion that lowering pain intensity should be the goal of CNCP treatment has been questioned.[55, 64, 65] Instead, it has been suggested that the focus for CNCP management should be on improving the ability to function and quality of life.[55, 64, 65] There are similarities in recommendations for opioid prescribing in CNCP across guidelines published internationally.[66] These recommendations include optimisation of non-opioid therapy; not using opioids as first-line therapy for patients with CNCP; if opioids are trialled, regular clinical assessments of benefits and harms are necessary; excessive doses should be avoided (recommended restricting of oral morphine equivalent (OME) daily doses ranging from 90 to 100 mg/day); and discontinuation of opioids if important improvement in pain or function is not achieved after a trial.[55, 64, 65]

1.3.1 Paracetamol

Paracetamol is a non-opioid analgesic belonging to step 1 of the WHO analgesic ladder.[58] Although paracetamol has been on the market since 1950,[67] the mechanism of action is complex and still not fully understood.[68] Paracetamol effects include "both peripheral (cyclooxygenase (COX) inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/nitric oxide pathway, cannabinoid system) antinociception processes and redox mechanism".[68] There is still ongoing debate about the role of COX-3 in its mechanism of action.[68] It is an effective mild analgesic but may not be effective for all types of pain. Paracetamol is effective for postoperative dental pain.[69] Paracetamol is also effective for headache, but it is less effective than other analgesics e.g., non-steroidal anti-inflammatory drugs (NSAIDs).[70] According to a collection of Cochrane and systematic reviews, there is insufficient evidence to support or refute the suggestion that paracetamol is effective in managing chronic pain.[71-74] However, it is still the most widely used over-the-counter analgesic worldwide.[75-77] In general, paracetamol is considered to have a better side effect profile than other analgesics, but there are concerns of adverse effects including acute liver failure at the higher end of the standard dose range.[78] Additionally, paracetamol can lead to death if taken in overdose.[75, 78]

1.3.2 NSAIDs

NSAIDs are non-opioid analgesics belonging to step 1 of the WHO analgesic ladder.[58] NSAIDs act by inhibiting COX1 and COX2 enzymes.[79, 80] COX-1 and COX-2 enzymes are involved in prostaglandin synthesis, therefore inhibiting this action results in the analgesic, anti-inflammatory, and antipyretic effects.[79] NSAIDs are commonly used worldwide, however incidence and prevalence rates vary depending on definitions used.[81-83] They are considered first-line therapy for many pain conditions including migraines, rheumatoid arthritis, and gout. There are two types of NSAIDs, non-selective NSAIDs which inhibit both COX1 and COX2 enzymes (e.g. ibuprofen) and COX2-inhibitors which are preferentially selective for COX2 (e.g. celecoxib).[79, 84] Although the two types of NSAIDs provide comparable analgesia, the differences in mechanism is key to the differences observed in adverse effects.[84] Non-selective NSAIDs

increase the risk of upper gastrointestinal (GI) adverse events (bleeding, ulcers, perforations).[84] COX2 selective inhibitors are associated with less GI events compared to nonselective NSAIDs.[84] However, COX2 inhibitors are associated with an increased risk of vascular events (non-fatal and fatal myocardial infarction).[85] A 2013 meta-analysis found that vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to COX2 inhibitors.[86] The meta-analysis also found that COX2 inhibitors also increase the risk of GI events, but to a lower extent than non-selective NSAIDs.[86] The use of long-term NSAIDs are limited by serious GI and vascular adverse events. Other serious adverse effects include renal impairment and heart failure.[86] Contraindications to NSAIDs and concern about these adverse events can be linked, in part, to increasing opioid use.

A recent meta-analysis included nine moderate-quality randomised controlled trials (RCTs) (1431 people) investigating opioids vs NSAIDs for CNCP.[87] The meta-analysis found no difference in pain relief between opioids and NSAIDs.[87] The same meta-analysis included seven moderate-quality RCTs (1311 people) and found no difference between opioids and NSAIDs in physical functioning assessed using the 100 point SF-36 physical component scale (composed of 8 multi-item scales that can be aggregated into two summary measures: the Physical and Mental Component Summary scores).[87] Additionally, five high-quality RCTs (2632 people) were included and showed an increased risk of vomiting with opioids compared to NSAIDs (Risk Ratio (RR)=4.71, 95% confidence interval (CI), 2.92-7.60).[87]

1.3.3 Opioids

The opioid class of medicines includes natural opiates (e.g., morphine, codeine), semi-synthetic opioids (e.g., oxycodone, hydromorphone, hydrocodone), and synthetic opioids (e.g., methadone, buprenorphine, and fentanyl).[88] Opioids mimic the actions of endogenous opioids by acting on opioid receptors in the central nervous system (CNS) and GI tract.[89, 90] They act mainly at mu-opioid receptors, but also on delta and kappa receptors in the CNS to produce analgesia.[90] This causes a reduction in the transmission of the pain impulse, and modulates the descending

inhibitory pathways from the brain.[89] Binding to the mu-opioid receptor can also activate central dopamine reward pathways and may be involved in euphoria.[90]

After morphine's isolation in 1806, it was the most commonly used opioid analgesic worldwide.[3] Opioid use largely depends on many factors including the geographical location, availability, legislative restrictions, prescriber and patient characteristics. In Australia, medicines and poisons are classified into Schedules according to the level of regulatory control over the availability of the medicine or poison required to protect public health and safety. Low dose codeine was available without prescription until February 2018. Due to legislative changes, all codeine analgesics are now only available on a prescription. This legislative change is important because this thesis was commenced before the change occurred. Low dose codeine combination products (<30 mg) were classified as Schedule 3 (Pharmacist Only Medicine) and have now been re-scheduled to Schedule 4 (Prescription Only Medicine).[91] Tramadol is also a Schedule 4 medicine, while single ingredient codeine and all other opioid analgesics are Schedule 8 (Controlled Drug) medicines in Australia.[91] Schedule 8 medicines are substances that should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.[91] Currently in most countries, including Australia and Sweden, opioid analgesics are available only by prescription. The term 'prescription opioid analgesics' refers to opioid analgesics prescribed to treat pain. This excludes illicit opioids e.g., heroin, and opioids used as opioid substitution therapy (e.g., buprenorphine and methadone).

Opioids can be categorised as weak and strong depending on their potency. Table 2 shows the weak and strong opioids available in the medicine databases during the study period for Australia and Sweden, respectively. Weak opioids include opioids in step 2 of the WHO analgesic ladder (e.g., codeine and tramadol). Strong opioids are those in step 3 of the ladder (e.g., morphine, oxycodone, fentanyl).[58] Opioid analgesics may provide a broad range of benefits including alleviating pain and improving quality of life.[88] The role of opioids in acute[2] and cancer[25] pain is well established. As has been highlighted, the use of opioids to treat CNCP remains

controversial.[26] The specific controversies will be further discussed in the section describing patterns of opioid use. Due to opioid's psychotropic effects e.g., euphoria, they are not always used in the manner in which they were intended when prescribed. Harm is partly attributed to diversion and extramedical use of opioids.

Table 2. Opioids available in the Australian and Swedish medicine databases during the study periods included in this thesis.

Australia[1]		**Sweden[2]**	
Strong opioids	**Weak opioids**	**Strong opioids**	**Weak opioids**
• Morphine	• Combination codeine preparations	• Morphine	• Combination codeine preparations
• Hydromorphone	• Tramadol	• Hydromorphone	• Tramadol
• Oxycodone	• **Tapentadol**	• Oxycodone	• **Dextropropoxyphene**
• Oxycodone/naloxone		• Oxycodone/naloxone	• **Tilidine**
• Fentanyl		• Fentanyl	• **Pentazocine**
• Buprenorphine		• Buprenorphine	
• **Methadone[3]**		• **Ketobemidone**	

Differences in opioid availability between Australia and Sweden are bolded.

[1]Opioids listed on the PBS between 2012 and 2018.

[2]Opioids available on the National Pharmaceutical Benefits Scheme in 2009 in Sweden.

[3]Methadone used for pain, not for opioid substitution therapy.

1.3.4 Other analgesics

A meta-analysis of 96 RCTs published in December 2018 compared the efficacy of opioids with other analgesics for CNCP with treatment lasting up to 6-months.[87] The review found low to moderate quality evidence that opioids are associated with similar improvements in pain and

physical functioning compared with tricyclic antidepressants and synthetic cannabinoids and are associated with small improvements in pain (weighted mean difference: −0.90 cm [95% CI, −1.65 to −0.14 cm] on the 10-cm visual analogue scale for pain) but not physical functioning compared with gabapentinoids (gabapentin and pregabalin).[87]

1.4 Patterns of opioid use

The type, formulation, dose, duration and indication of opioid use have changed over the past three decades. Worldwide opioid use has more than doubled in just one decade,[18] however differences in patterns of opioid use exist across jurisdictions and countries.[18] The US and Canada are in the midst of an "opioid crisis" driven by both prescription and illicit opioids,[92, 93] while most low income countries have limited availability and access to prescription opioids.[18, 94] International differences in opioid use are likely to stem from differences in culture, health care systems, health care availability and access, clinical practice standards and promotional activities by pharmaceutical industries.[55, 95] The CDC has identified three 'problematic' patterns of opioid use including excess opioid use, long-term, and high-dose opioid use that have been attributed to the increased opioid-related harms.[29, 96] These patterns of opioid use have formed the framework for the studies conducted in Chapters Three to Five of this thesis. These high-risk patterns of opioid use and gaps in the literature are discussed below highlighting the use in Australia, US, Canada and Western Europe. Patterns of opioid use in Sweden are also specifically presented.

1.4.1 Methods for measurement

With increasing opioid use worldwide, consistent methods or units of measure are required to compare utilisation patterns across jurisdictions and countries. The most commonly used unit of measure for dose in drug utilisation studies is the WHO's unit Defined Daily Doses (DDDs). DDDs are defined as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'.[97] Although DDDs are widely used, they do not reflect the relative clinical potencies of opioids. This is because DDDs provide an estimate of consumption and not the actual dose used.[97] This is important for opioid utilisation as opioids have highly individualised

dosing regimens and different potencies. The recognition of this prompted researchers to use OMEs.[98, 99] This is a unit of measure that takes into account this variability.[98, 99]

OMEs refer to the total dosage or amount of opioids used accounting for differences in opioid type and strength. This is based on the concept that different doses of different opioids (with varying potency) may produce a similar analgesic effect.[91] Equianalgesic doses are doses whereby two different opioids are considered to give a comparable analgesic effect.[91] The equianalgesic ratios or OME conversion ratios for the same opioid are not always consistent in the literature, making comparison difficult between studies.[99] However, Nielsen et al[91] developed a comprehensive OME conversion table in order to enable consistent calculation of OMEs when undertaking pharmacoepidemiological studies of opioids. These OME conversion ratios have been employed throughout the research undertaken in this thesis.

1.4.2 Opioid utilisation

Opioid analgesic use has increased exponentially over the past two decades according to the International Narcotics Control Board (INCB).[18] The increase in opioid analgesic use has been largely attributed to an increase in prescribing for CNCP.[14-17] Without adjusting for population changes, worldwide opioid use has doubled in absolute terms from 3.0 billion defined daily doses for statistical purposes (sDDDs) per annum in 2001– 2003 to 7.3 billion DDDs per annum in 2011–2013.[18] The INCB data comprises national aggregated data reported as kilograms and converted to DDDs. These data exclude codeine combinations and tramadol reporting is not mandated.[100] Therefore, global opioid consumption is likely higher.[100]

According to the INCB, the majority of the opioid increase has been driven by opioid utilisation in the US, Canada, Western Europe, Australia and New Zealand. These countries collectively account for 92% of the overall opioid utilisation but only 17% of the world's population.[101] This large disparity in opioid use internationally,[18] suggests a potential overuse in some countries and underuse in others. Berterame et al. found that low levels of opioid consumption in most

low-income countries do not reflect the prevalence of health disorders (e.g. cancer) warranting opioid use.[18] This suggest a lack of opioid availability and access even for palliative care in low income countries.[94]

A reduction in opioid analgesic use has been observed in Africa, from 50 sDDDs/million people/day in 2001– 2003 to 41 sDDDs/million people/day in 2011–2013.[18] During the same time, opioid use in the US doubled from 22,554 sDDDs/million people/day to 43,879 sDDDs/million people/day.[18] A four-fold increase in opioid analgesic use has been observed in Australia, from 3287 sDDDs/million people/day in 2001– 2003 to 13,440 sDDDs/million people/day in 2011–2013.[18] During the same time, opioid analgesic use increased by two-fold in Sweden, from 3,342 sDDDs/million people/day to 8,343 sDDDs/million people/day.[18] Given the high use of opioids in Australia, this thesis will mainly focus on issues associated with high opioid use and will compare these issues mainly across countries with high opioid use.

In 2016-17, 15.4 million opioid prescriptions were dispensed under Australia's Pharmaceutical Benefits Scheme (PBS) to 3.1 million people.[1] In total, approximately 21.3 million opioid prescriptions were dispensed in Canada in 2017.[102] The number of opioid prescriptions dispensed per 1000 population in Canada has slightly reduced from its peak in 2015 from 600 prescriptions to 582.[102] The total number of opioid prescriptions dispensed in the US peaked in 2012 at approximately 255 million and reduced to approximately 191 million in 2017.[21, 103] This equates to prescribing rates of 81.3 to 58.7 prescriptions per 100 persons in 2012 and 2017, respectively.[103] The proportion of individuals ≥30 years dispensed ≥1 opioid prescription was largely constant between 2000 and 2015 (114 to 112 per 1 000 population) in Sweden.[104] This may mean that the doubling in opioid consumption in Sweden as reported by the INCB[18] may be due to higher doses, strong or long-term opioid use rather than increased prevalence. However, this has not been investigated in Sweden to date.

In addition to increases in overall rates of opioid use, shifts in the type of opioids and ratio of strong to weak opioids has occurred (Figure 1).[100, 104-107] The introduction of long-acting opioid formulations has resulted in an increase in prescribing of long-acting opioid formulations, with 15.2 million prescriptions and 24.1 million prescriptions dispensed annually in the US in 2002 and 2016, respectively.[108] Presently, fentanyl, hydrocodone and oxycodone account for the majority of global opioid use.[100] The use of these three opioids has increased 5-10 fold between 1995 and 2015.[100] In recent years, the number of opioid prescriptions dispensed have started to decline in the US (12.8% decline between 2011 and 2016)[108] and Canada (1.8% decline between 2016 and 2017).[102] Nevertheless, in the US a total of 56,935,332 people, or 17.4% of the population, filled ≥1 prescription for an opioid in 2017.[21]

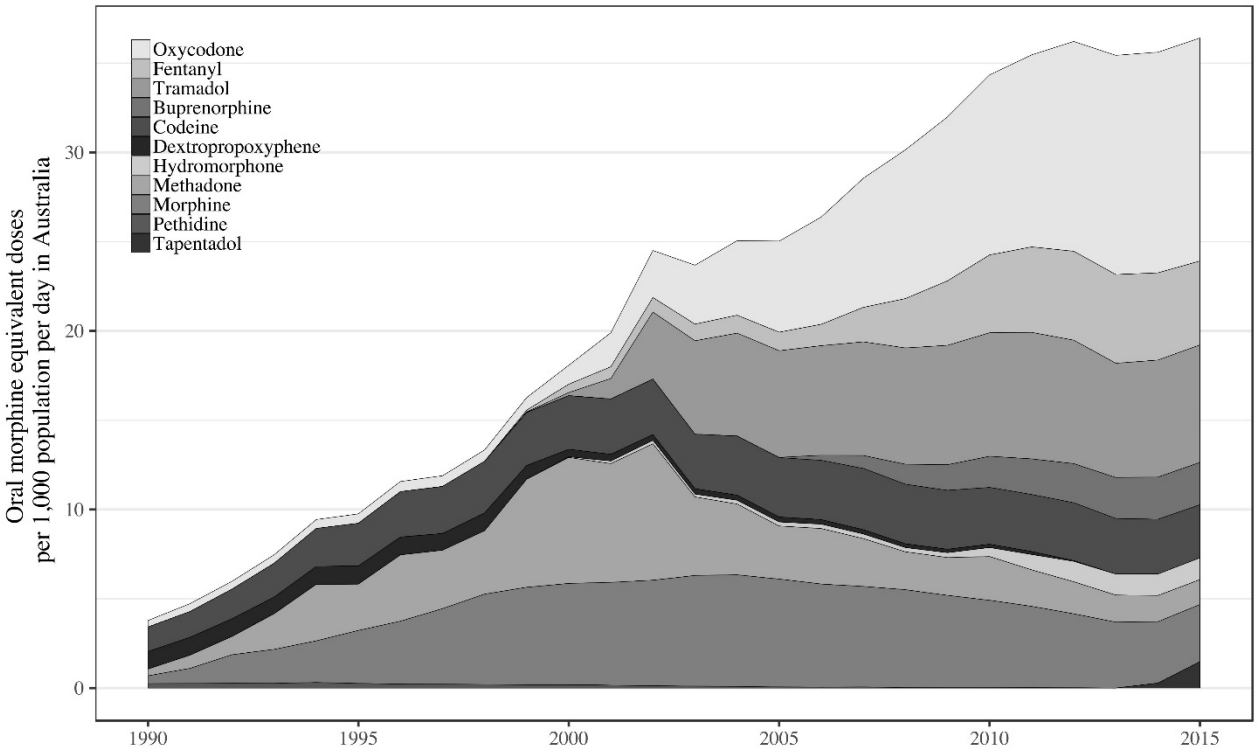

Figure 1.* Trends in opioid utilization (using pharmaceutical claim data) as expressed in oral morphine equivalent doses per 1000 population per day in Australia, 1990–2015.

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1.4.3 Long-term or persistent opioid use

The definition of persistent opioid use is inconsistent in the literature.[109] This term is often used interchangeably with long-term and chronic use.[109] The definitions reported in the literature may

include one or more variations of the following criteria: duration of opioid use, number of opioid prescriptions, acceptable gaps between prescriptions, total yearly amount in DDDs or OMEs.[17, 109, 110] A Norwegian study found that there is no single appropriate definition for persistent opioid use when using explicit criteria.[109] Defining opioid persistence is challenging because daily doses of opioids vary widely among patients and also over time. The incidence and prevalence of persistent opioid use varies markedly depending on the definition used and the population investigated (e.g., among all patients initiating opioids compared to patients with chronic pain treated at a pain clinic). This makes it difficult to compare studies directly. Nonetheless, long-term opioid use is associated with the development of tolerance to the analgesic effect, dependence, drug diversion and overdose.[14, 111] Long-term opioid use (>3 months) is associated with a 5.5% risk of dependence at low doses (<20mg OMEs/day), a 0.2% risk of non-fatal overdose and a 0.1% risk of fatal overdose.[28] A review by Chou et al. found that there were currently no RCTs published investigating opioids vs placebo or non-opioid therapy for chronic pain that evaluate long-term (≥1 year) outcomes related to pain, function, or quality of life.[26, 29] Persistent opioid use at a population level had not been studied in Australia, therefore it is unclear how opioid persistence compares to other countries. This gap in the literature formed the basis for the study in Chapter Four of this thesis.

1.4.4 Dose escalation

Dose escalation refers to an increase in opioid dose prescribed or used over time in a given individual, usually it occurs in a stepwise manner. Dose escalation occurs when the response to opioids is inadequate and may be due to the development of tolerance (a psychological adaptation) to opioid therapy. This results in a need for increased doses to get the same effects, or the loss of effectiveness at a given dose.[112] Other reasons for opioid escalation include underlying disease progression and the development of opioid use disorder.[113] Various definitions have been used to define opioid dose escalation in the literature. In a study investigating 246 people, 9% of people experienced dose escalation (defined as an increase in mean daily opioid dose of ≥30mg OMEs over 1-year).[114] People with dose escalation had higher rates of substance

use diagnoses (17% vs 1%, p=0.01) and more total outpatient encounters (51 vs 35, P = 0.002) over 1- year compared to those without escalation.[114] A RCT by Naliboff et al[115].found no difference in pain, function and use of non-opioid therapy between more liberal dose escalations (increased when deemed medically necessary) compared to maintenance of current doses after 12-months. However, the mean difference in OME dose in mg/day at the end of the trial was 17mg/day between the two groups.[115] The 'escalating group' showed an 80% increase in opioid dosage over the 12-months, whereas the 'stable dose' group showed only a 16% dose increase.[115] A retrospective cohort study of patients with chronic pain, reported that patients <50 years escalated their dose on average by 27mg OMEs/day per month, while patients >60 years escalated at a substantially slower rate of 12 mg OMEs/day on average per month during a 15-month period.[113] These studies were conducted prior to recommendations of dosing thresholds by international guidelines, including the CDC,[29] Canadian[28] and Australian guidelines.[27] Additionally, in Australia, currently there are no published studies investigating opioid dose escalation. This is an important research question to address because dose escalation in the US has been associated with increased risks of harm.[114] This gap in the literature steered the research aims for Chapter Five of this thesis.

1.4.5 High dose opioid use

High-dose opioid use has been associated with increased falls, fractures, hospitalisation, motor vehicle injury and opioid-related overdose and death.[14, 15, 27, 116-119] Definitions of what constitutes high dose opioids vary in the literature (range 50-200 mg OMEs/day), [14, 15, 116-119] making prevalence comparison between studies difficult. Current US[29] and Canadian[28] guidelines for prescribing in CNCP suggest that increasing dosage to ≥90 mg OMEs/day should be avoided or the decision to titrate dosage to ≥90 mg OMEs/day should be carefully justified.[28, 29] The 2017 Royal Australian College of General Practitioners *'The role of opioids in pain management'* guideline suggests dosage ≥100 mg OMEs/day should be avoided.[27] There have been no studies investigating high dose opioid use in Australia. Taking into account the increased harm associated with high dose opioid use reported in the US and Canada,[14, 15, 27, 116-119] investigating

patterns of high dose use is important in Australia. This gap in high dose use, along with the gaps investigating dose escalation guided the study in Chapter Five.

1.4.6 Concomitant use of psychotropic medicines

Concomitant use of psychotropic medicine, most commonly benzodiazepines, in people prescribed opioids has been associated with an increased risk of overdose deaths.[119-131] Administration of opioids with other CNS depressants can increase risk of over-sedation and respiratory depression.[132] Current guidelines recommend that concurrent use of benzodiazepines and opioids should be avoided wherever possible.[27-29] In Australia, concomitant psychotropic medicine use is commonly reported in opioid related overdose deaths .[123, 130, 131] Pilgrim et al reported that 63.4% (n=511) of oxycodone related deaths investigated by the coroner were attributed to multiple or combined drug toxicity as the cause of death.[131] A large prospective cohort study in North Carolina (n= 2,182,374) found that of all opioid analgesic recipients, 80% were also prescribed a benzodiazepine in the past year.[119] Of opioid-related overdose deaths, benzodiazepines were determined to be involved in 61.4% (n=386) of cases.[119] A recently published cohort study found that the number of people concomitantly dispensed benzodiazepines and opioids declined from 93 630 (14.8% of people dispensed opioids) in July 2012 to 91 550 (12.7%) in June 2017 in Australia.[133] Concomitant use was defined as a benzodiazepine being dispensed to an individual within a week of being dispensed an opioid.[133]

Recently, gabapentinoid (pregabalin and gabapentin) use has expanded to include use as an alternative or adjunctive therapy to opioids for CNCP.[134-136] Consequently, concomitant use of gabapentinoids and opioids has increased.[128, 137] There is concern about an increased risk of respiratory depression and overdose with concomitant use of gabapentinoids and POAs. Among patients receiving POAs in Canada, concomitant use of gabapentin or pregabalin was found to increase the risk of opioid-related death compared to opioid use alone.[128, 138] Recent studies in Australia suggest that pregabalin rarely causes death when used alone and that most deaths are due to combination use with opioids.[137, 139] Identifying the characteristics of those prescribed

opioids and other CNS acting medicines along with patterns of prescribing may aid in formulating interventions to mitigate risks. For this reason, prior gabapentinoid and psychotropic use was a consideration for all the studies conducted in this thesis.

1.4.7 Extramedical opioid use

Extramedical opioid use refers to use in a manner that is different to the prescriber's intention or accessing prescription opioid analgesics outside of the formal medical system.[140] This includes use without a prescription; use in greater amounts, more often, via a different route or longer than advised to take a medicine; or use in any other way not directed by the presciber.[21, 140] This definition does not exclude the possibility that the user may have a medically driven reason for using the opioid in a different way to that intended by the prescriber.[140] The term extramedical use may be synonymous with misuse and non-medical use in the literature. In 2016, an estimated 11.5 million or 4.3% of people aged ≥12 years in the US reported extramedical use of prescription opioid analgesics in the past year.[21] The Australian National Drug Strategy Household Survey found that an estimated 3.6% of people, or approximately 700,000 people aged ≥14 years in 2016 reported extramedical use of opioid analgesics in the past year in Australia.[1, 58, 141] Of those that used opioids extramedically, one third also used illicit substances.[141] In 2017, among the 3.5 million people using opioids in Canada, 3% or 100,000 reported extramedical use in the past year.[142] There were approximately 1.3 million adult 'high-risk' opioid users in the Europe Union countries in 2015.[143] Germany, Spain, France, Italy and the United Kingdom account for 76% of these 'high-risk' opioid users.[143] The definition of 'high-risk' opioid use varies across the European countries and may include illicit and licit opioid use, making it challenging to determine the number of people using prescription opioids extramedically. There are also limited data on extramedical prescription opioid use in many low-middle income countries. However, there is increasing evidence of extramedical use of tramadol and codeine in Africa.[144]

A systematic review investigating rates of extramedical opioid use in people with CNCP found that prevalence rates averaged between 21% and 29% (range 95% CI 13%–38%).[145] All the

studies investigating extramedical use were from the US, except one study conducted in Norway that reported rates of extramedical use between 0.08-0.3.[145] A narrative review found an association between extramedical use of opioids and chronic pain and mental health conditions, particularly depression and anxiety disorders.[146] Based on the 2015 National Survey on Drug Use and Health in the US, 63.4% of adults reporting extramedical prescription opioid analgesic use described that their motivation for extramedical use was to relieve physical pain.[147]

In the US and Canada, the harms associated with opioid use have been partly attributed to extramedical prescription opioid analgesic use and include increased health-care utilisation including hospitalisation,[148-150] transition to heroin,[151-155] and fatal and non-fatal overdose.[14, 150, 156] A recent study found that the demographic composition of heroin users entering treatment in the US has shifted over the last 50 years.[155] People who began using heroin in the 1960s were predominantly young men whose first opioid of abuse was heroin (80%), however, more recent users were older men and women who were introduced to opioids through prescription medicines (75.0%).[155] Although the Australian National Drug Strategy Household Survey suggests similar rates of extramedical use in Australia and the US, a comprehensive review of the types of harm and risk factors for extramedical prescription opioid analgesic use in Australia have not been investigated. This gap in the literature formed the basis of Chapter Two of this thesis.

1.5 Summary of high-risk patterns

The patterns of opioid use discussed in section *1.4 Patterns of opioid use* and summarised below in Table 3 contribute to increased opioid-related harm. These patterns of opioid use are not often seen or reported in isolation in clinical practice. Although some of these patterns have been studied in the US and Canada, there is limited research on these high-risk patterns on an individual level in Australia. These patterns of opioid use have been largely attributed to use for CNCP.

Table 3. Summary of patterns of opioid use associated with harms and the gaps identified in the Australian literature.

Pattern of opioid use	**Associated harm**	**Gaps in the Australian literature**
Excess prescriptions	Fatal and non-fatal overdose deaths,[15, 19, 20, 24, 157-160] ambulance attendances,[121] emergency department visits,[24, 161] hospitalisation,[19, 20] and opioid use disorder[20]	Population-based individual level incidence and prevalence of opioid use has not been investigated
Long-term use	Tolerance to the analgesic effect,[111] dependence,[2, 111] drug diversion and non-fatal and fatal overdose[14]	Population-based individual level studies have not investigated long-term opioid use
Dose escalation	Increased healthcare utilisation[114] and dependence[114]	Population-based individual level studies have not investigated opioid dose escalation
High dose use	Fractures,[117] hospitalisation,[118] motor vehicle injury[116] and opioid-related overdose[27] and death[14, 15, 119]	Population-based individual level studies have not investigated high dose opioid use
Extramedical use	Health-care utilisation including hospitalisation,[148-150] transition to heroin,[151-154] and fatal and non-fatal overdose[14, 150, 156]	Synthesis of harms associated with extramedical use does not exist in Australia
Concomitant use with other psychotropic substances	Over-sedation, [132] respiratory depression,[132] overdose deaths[119-129, 137]	Reported in coronial studies, but has not been studied among people initiating opioids using whole population data in Australia

During the mid-20th century, new opioid analgesics and formulations were introduced onto the market and were targeted for use in CNCP. As new opioids and formulations were going to be investigated for non-approved indications, efficacy needed to be compared to an opioid approved for clinical use at the time (morphine). Subsequently, systematic reviews and meta-analyses of various RCTs investigating opioids for CNCP were conducted.[111, 162-165] Evidence from individual trials and reviews showed that short-term efficacy of opioid analgesics was good.[111, 162-165] However, findings on functional improvement, health-related quality of life, abuse and dependence are mixed.[55] Further limitations include the short duration of studies limiting assessment of long-term efficacy and adverse outcomes. Additionally, the study participants were not eligible for inclusion if they were at risk of substance abuse. Existing studies confirmed early analgesic efficacy but did not provide information about 'real-world' opioid effectiveness, particularly long-term effectiveness. Nonetheless, opioids were prescribed to a broader-ranger of people with CNCP who may not have fulfilled the strict requirements of the RCTs. Subsequently, real-world evidence reported safety concerns associated with long-term opioid use, including development of tolerance to the analgesic effect, dependence and drug diversion.[14, 28, 111]

Opioid use, in particular long-term use, for CNCP remains controversial. Current US, Canadian and Australian guidelines provide recommendations on prescribing opioids long-term for CNCP due to minimal evidence for effectiveness and increased evidence of harm.[27-29] The guidelines recognise that clinical decision making for long-term opioid therapy is complex and requires individualised benefit-risk assessments. Additionally, opioid selection and dose initiation and titration strategies; integration of risk assessment and mitigation strategies; and ongoing review is suggested.[29] The challenges faced by many clinicians when it comes to management of CNCP with prescription opioid analgesics have been discussed in the above sections of this thesis. In addition to limited evidence for effectiveness and evidence of harm, the controversy over the use of prescription opioid analgesics for the treatment of CNCP has been heightened by evidence that long-term opioid use alters pain modulatory systems.[166, 167] This may lead to hyperalgesia (increased pain sensitivity) or aggravate the underlying pain condition.[166, 167] Although the above

patterns of opioid use are not recommended, they are still being prescribed, dispensed and used. Understanding the scale of these high-risk patterns of use in Australia is important for clinicians and health policy makers. Without this knowledge implementation of preventative strategies to reduce opioid-related harm may be misguided. As outlined in the individual sections above, currently, there are limited data on the patterns of opioid use at a patient-level in Australia

1.6 Work related outcomes

CNCP is a leading cause of disability worldwide[46] CNCP often affects an individual's short and long-term capacity to work.[168] A systematic review by Patel et al[169] reported that CNCP is a frequent cause of work disability, with between 13% and 76% of people with CNCP reporting work disability. This is because pain interferes with daily activities, physical and mental health, family and social relationships, and interactions in the workplace.[45] Indirect costs due to lost productivity because of SA and reduced work capacity are considerable and represent the largest proportion of the total costs of CNCP.[47-50, 72, 170] Therefore, optimising pain management is important to reduce disability and facilitate return to work. Improved quality of life and improved functional capacity are considered to be key outcomes of pain management. Yet, evidence suggests that opioid treatment of CNCP does not seem to fulfil any of these key outcome treatment goals.[171] Studies have also shown that the use of opioids is associated with high workers' compensation costs, prolonged disability after an injury, delayed functional recovery and return to work.[172-180]All of the studies investigating work disability and opioid use have used workers compensation data rather than nationwide data.[172-180] The effect of opioid initiation on work disability has not been studied at a population level. This type of study can only be conducted in countries with a nationwide public insurance system. The Swedish health system has similarities to the Australian health system. In addition, Sweden has linked dispensing data registers with the public insurance system data. Collaboration with Sweden was important to investigate the gap relating to work disability identified in the literature.

1.7 Opioid related harms

The increase in opioid prescribing is paralleled by an increase in overdose deaths, ambulance attendances, emergency department visits and opioid use disorder arising from both medical and extramedical opioid use.[19, 20, 24, 121, 157-161, 181] The US Department of Health and Human declared a public health emergency in response to the 'opioid epidemic'. The scale of opioid-related harm reported worldwide varies significantly. A recent report by the Australian Institute of Health and Welfare highlighted the various social and health-related harms resulting from opioid use.[1] This report showed that there were similarities between the harm seen in Australia and Canada. These harms and other opioid-related harms will be discussed in more detail below.

1.7.1 Overdose deaths

In the US, between 2001 and 2016, the number of overdose deaths related to prescribed and illicit opioids increased by 345%, from 9,489 to 42,245 deaths (33.3 to 130.7 deaths per million population).[182] The CDC reported that there were more than 17,000 overdose deaths involving prescription opioid analgesics in 2017, exceeding the 15,000 heroin-related deaths.[183] In Canada, between January 2016 and June 2018 there were 9,078 overdose deaths involving prescribed and illicit opioids.[184] Of these, 3,014 deaths occurred in 2016 and 3,998 in 2017.[184] Between January and June 2018, there were 2,066 opioid-related overdose deaths, of which 94% were accidental.[184] Currently delineation of prescribed and illicit opioid-related deaths is not possible on a national level in Canada.

The extent of opioid-related harms as observed in the US are considered uncommon in most of Europe.[181] Among Turkey, Norway, and the European Union Member States, 9138 drug-induced deaths were reported.[185] Of these, 78% had prescribed or illicit opioids present in toxicology reports.[185] In Australia, illicit and licit opioids have been the leading group of medicines contributing to drug-induced deaths for the last 20 years.[98] Although the rate of heroin overdose deaths has remained unchanged between 2001 and 2012 (13.2 to 14.5 per million population), opioid analgesic overdose deaths increased from 21.9 to 36.2 per million population during the

same period.[186] In 2016, there were 1,045 opioid-related deaths among Australians aged 15-64 years based on the data from the National Coronial Information System.[187] Opioid analgesic deaths were largely driven by accidental overdoses (85%).[187] The majority (65%) of all opioid-related deaths were due to pharmaceutical opioids in 2016.[187] A recent review did not identify literature on opioid overdose mortality rates in Africa.[144]

1.7.2 Health care resource utilisation

Opioid overdose or poisoning can require an ambulance attendance, care in the ED or a hospital admission.[1] In 2016-17, 77% of opioid poisoning presentations arrived by ambulance in Australia.[1] During this time, the number of ED presentations with a principal diagnosis of opioid poisoning was 4,232 (17.5 presentations per 100,000 population).[1] Furthermore, there were 9,636 hospitalisations (or 39.8 hospitalisations per 100,000 population) with opioid poisoning as any diagnosis and 4,234 hospitalisation as opioid poisoning as the principal diagnosis over the same period.[1] In 2016/17, there were 5,670 hospitalisations due to opioid poisoning in Canada.[188] Over the same period, there were 3,894 ED presentations in Alberta and 4831 ED presentations in Ontario due to opioid poisoning.[188] In the US, there were 58,090 opioid-related (excluding methadone and heroin) ED presentations in 2015.[21] Moreover, there were an estimated 174,100 hospitalisations due to opioid overdose in 2012-14.[189] In 2016, there were 243.5 opioid-related ED presentations per 100,000 population and 296.9 opioid-related hospitalisations per 100,000 population in the US.[190] In Europe, heroin use still accounts for the majority (approximately 80%), of new opioid-related treatment demands.[191] Similarly in Australia, heroin use still accounts for majority (61% or 9,988) of opioid-related treatment episodes in 2016-17, however this has decreased by 36% since 2007-08.[1] By contrast, treatment episodes doubled for codeine (from 628 to 1,233), and for oxycodone they tripled (from 305 to 911) over the same period.[1]

1.7.3 Opioid use disorder

Opioid use disorder (OUD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).[192] The term OUD replaced the terms opioid abuse and opioid

dependence used in DSM-4. However, there is only fair to moderate agreement between ICD-10 and DSM-IV dependence diagnoses, and DSM-5 OUD.[193] The criteria for OUD can by summarised by the presence of the three C's including control loss (out of control use), compulsivity (devoting substantial time to obtaining, using, and recovering from substances) and continued use regardless of adverse consequences.[192] In the US, almost 2 million people were estimated to meet the DSM-4 criteria for abuse and dependence in 2013.[194] Based on the 2015 National Survey on Drug Use and Health, 1.9 million adults were estimated to have an OUD in the US.[147] Of the 11.5 million adults reporting extramedical prescription opioid analgesic use, 16.7% reported an OUD.[147] The societal economic cost associated with OUD in the US is estimated at $78.5 billion annually.[194] In Australia, 0.2% of adults surveyed met criteria for an OUD in the past 12 months.[195] Additionally, there were 566 ED presentations and 16,903 hospitalisations in 2016-17 for opioid dependence in Australia.[1] The prevalence of OUD among people who take opioids long-term ranged from 20.8% to 34.9% in the literature.[193, 196, 197]

1.7.4 Other harm

Although overdose mortality is the most dramatic consequence from opioid use, there are other risks associated with opioid use. These include falls,[198-203] fractures,[199, 201, 204-207], depression,[185] GI adverse effects,[198, 208-210] cardiovascular events,[211-213] hormonal dysfunction,[214-217] and road trauma.[116] Additionally, opioid induced hyperalgesia (OIH) can occur and is difficult to diagnose in clinical practice.[218] This is a phenomenon that results in increased sensitivity to pain due to opioid exposure or a paradoxical pain hypersensitivity.[218] It may present as worsening pain despite increasing opioid doses, worse or diffuse pain that cannot be explained by the progression of the original condition causing pian.[218] This is different to physiological dependence whereby the body relies on the opioid to maintain biochemical homeostasis.[112] If the opioid is not available or given at a lower dose, the body becomes biochemically dysregulated and this manifests as withdrawal.[112] Symptoms of opioid withdrawal include arthralgias, myalgias, diaphoresis, nausea, vomiting, muscle and bone pain.[112] OIH is also different to tolerance, whereby a progressive lack of response to opioids can be overcome by increasing the dose.[219]

1.8 Strategies to reduce high-risk opioid prescribing and minimise harm

Various strategies have been employed globally to prevent the harm associated with increased opioid prescribing and use.[63, 204, 220-224] To date, no single intervention has been adequate on its own to reduce the overall harm related to prescription opioid analgesic use.[224] Strategies that have been trialled or implemented include prescriber and community education and awareness campaigns, use of medicine-assisted treatment (e.g. opioid substitution therapy), implementation of prescribing standards, guideline and policy implementation, restricting supply, implementing prescription drug monitoring programmes (PDMPs), support programs for people with pain, increasing availability and access to multidisciplinary programs, introducing misuse-deterrent opioid formulations, and expanding naloxone distribution and access.[63, 220-224] A systems approach that aligns with the broader health-care, policy and legal systems, while balancing individual benefits and risks, is required to order to address the 'opioid epidemic'.[225]

A recently published perspective piece outlined the regulatory and other responses implemented to data in Australia to minimise the pharmaceutical opioid problem.[221] A National Pharmaceutical Drug Misuse Framework for Action (2012-2015) was formed to address the increasing opioid use and harms in Australia.[226] This was a holistic approach that considered the complex range of factors that contribute to the extramedical use of medicines.[226] Possible strategies to minimise harm were highlighted including PDMPs, education and training of health professionals, re-scheduling of medicines, improvement of access to pain and addiction services, and development of resources including guidelines.[226] Currently, few of these strategies have been implemented nationally.[221] Examples of strategies that have been implemented include restricting codeine use by rescheduling to Schedule 4 in February 2018, introducing PDMPs in Tasmania (DORA) and Victoria (SafeScript), increasing access of naloxone by rescheduling to include over-the-counter access (Schedule 3) and increasing education and awareness about opioid-related harms.[221]

1.9 Access to medicines

Differences in health care systems exist around the globe. Since this thesis analysed general populations from Australia and Sweden who used prescription opioid analgesics, these two health care systems are discussed below with a primary focus on access to medicines and more specifically access to prescription opioid analgesics. This section provides further context for the two populations studied in this thesis.

1.9.1 Access to medicines in Australia

Health care in Australia is largely government funded (69% in 2016-17).[127] Non-government organisations, private health insurers, and individuals who pay for some services out of their own pockets contribute to the remainder of health expenditure. Health expenditure accounted for 10% of the gross domestic product (GDP) in 2016-17.[127] Medicare is a publicly funded universal healthcare system operating in Australia. This universal healthcare system entitles all Australian citizens and permanent residents to free or subsidised healthcare including prescription medicines.

The National Medicines Policy (NMP) was established in 1999 and aims to improve positive health outcomes for all Australians through their access to and wise use of medicines.[227] Quality use of medicines (QUM) is one of the central objectives of the NMP. The central objectives of QUM are: selecting management options wisely, choosing suitable medicines if a medicine is considered necessary; and using medicines safely and effectively. The government subsidises the cost of medicine for most medical conditions under the Pharmaceutical Benefits Scheme (PBS). Most opioid analgesics are subsidised under the PBS, though various restrictions apply depending on the formulation and type of opioid. Concessional beneficiaries (e.g. pensioners and low-income earners) are entitled to subsidised rates on all PBS-listed medicines and pay a reduced co-payment amount. The co-payment amount for concessional beneficiaries in 2019 is $6.50 per prescription,[228] up to $390 per year.[229] At this point, the safety net threshold is reached and the concessional beneficiary does not pay the co-payment amount for the rest of that

calendar year. General beneficiaries are entitled to subsidised rates on higher-cost medicines priced above a set co-payment amount. The co-payment amount for general beneficiaries in 2019 is $40.30, up to $1550.70 per year.[228] At this point, the safety net threshold is reached and the general beneficiary pays the concessional co-payment amount of $6.50 per prescription for the rest of that calendar year. The same thresholds above can apply to a family.[229] The PBS is part of the broader NMP.

Most of the medicines listed on the PBS are dispensed by pharmacists and used by patients at home. There are medicines that are approved for use by the Therapeutics Goods Administration (TGA) but not listed on the PBS. These medicines can be obtained privately. Until February 2018, all low-dose codeine products were available over-the-counter. For private or over-the-counter medicines, the patient pays the full cost for that medicine. If a patient requires larger quantities of subsidised opioids than authorized by the PBS, the prescriber can prescribe these opioids privately. The PBS data does not capture private prescriptions, over-the-counter medicines, medicines dispensed to inpatients in public hospitals, and prior to July 2012 it did not capture prescriptions under the co-payment amount. For general beneficiaries, most of the opioid prescriptions are below the co-payment amount and therefore were not captured in PBS data prior to July 2012. For example, under the PBS in 2019, 20 capsules of oxycodone immediate release 5mg cost $22.48 for general beneficiaries (under the co-payment as below $40.30). Capturing under co-payment data, had important implications for analysis of opioid use in Australia at an individual level in this thesis. As of 2014, the PBS data were estimated to capture more than 80% of all opioid prescriptions dispensed in Australia.[230]

1.9.2 Access to medicines in Sweden

Healthcare in Sweden is largely government funded.[231] Similar to the Australian health care system, it is a system that ensures everyone has equal access to healthcare services. Health expenditure in 2014 represented 11% of GDP.[231] Approximately 83% of this spending was publicly funded in 2014.[231] Approximately 16% of all health expenditure was privately funded. [231]

This included 97% out of pocket expenses, the majority of which were for medicines.[231] Private health insurance financed approximately 1% of the health expenditure in 2014.[231]

In Sweden, a National Pharmaceutical Benefits Scheme exists for reimbursement of medicines. Adults pay the full cost of prescription medicines up to SEK 1,100 ($170 AUD) annually.[231] Subsequently a subsidy is applied which gradually increases to 100%, with the maximum annual out-of-pocket expenses totalling SEK 2,200 ($340 AUD).[231] A separate out of pocket maximum applies to children belonging to a family.[231] Similar to the PBS in Australia, certain medicines are not available on the National Pharmaceutical Benefits Scheme and are not subject to reimbursement.[231] Therefore the individual pays the full price for the medicine. All medicines subsidised by the National Pharmaceutical Benefits Scheme are captured in the Swedish Prescribed Drug Register. All opioids are available only via a prescription in Sweden and included in the Swedish Prescribed Drug Register. The Swedish Prescribed Drug Register provides complete national data on medicines dispensed in the Swedish population.[232] Similar to the Australian PBS data, the Swedish Prescribed Drug Register does not capture over-the-counter medicines and medicines dispensed to inpatients in hospital.[232] However, it is estimated that 84% of all medicine utilisation in Sweden is captured by the Swedish Prescribed Drug Register.[232]

1.10 Use of administrative databases

Administrative databases contain data collected primarily for purposes other than research.[233] These include data routinely collected by governments, healthcare providers and insurers.[234] The use of these data sources is becoming increasingly important in research because these data allow for linkage over time and across data sources to create longitudinal records for individuals.[233] Furthermore, administrative data sources can assess rare or uncommon adverse events, examine medicine safety and patterns of medicine use. This is particularly useful when medication use is possibly subject to recall bias or underreporting e.g., opioids. Researchers can analyse real-world data and are not restricted by strict RCT inclusion criteria. Administrative data can be particularly useful for investigating medicine use in groups that are commonly excluded

from RCTs including people with substance dependence, older people, children and pregnant women. The majority of the harms reported in section *1.7 Opioid related harms* of this thesis were findings obtained from administrative data sources, including ED presentations, hospitalisations and deaths.

It has been suggested that improved access to PBS data could provide an efficient and cost-effective way to monitor use of prescription opioid analgesics.[235] This thesis utilises PBS data for studies in Chapter Three to Five and Swedish Drug Register data linked with health and social insurance, death and cancer registry data for the study in Chapter Six. Table 4 below outlines the strengths and limitations of using the 10% random sample of the PBS data for research purposes. Table 5 outlines the strengths and limitations of using the Sweden Drug Register for research purposes. These data sources are important for investigating individual-level medicine use in a whole population. Administrative data sources have been widely used to provide real-world data on opioid use and outcomes, particularly in the US.[236-241] Similar whole population studies were not possible to conduct in Australia until recently, because the under co-payment data were not included. Therefore, the studies in this thesis investigated opioid use, patterns and predictors that were not previously possible to undertake in Australia prior to July 2012.

Table 4. Strength and limitations of the 10% random sample of PBS data for research purposes.

Strengths	**Limitations**
Captures majority of the real-world dispensings in Australia	Private prescriptions, over the counter medicines and inpatient dispensings are not captured
Medicines dispensed by public hospitals on discharge or as an outpatient are captured in most states and territories	Medicines dispensed by public hospitals on discharge or as an outpatient are not captured in New South Wales or the Australian Capital Territory
Random 10% sample considered representative of the whole Australian population	Limited sociodemographic variables included
Individual-level data including age, sex, year of birth, year of death, derived prescriber speciality, patient category (e.g., concessional), PBS item codes for medicines	PBS item codes may change overtime, therefore these changes need to considered when undertaking pharmacoepidemiological research
Since July 2012, under co-payment data is captured	Prior to July 2012, data needs to be restricted to concessional beneficiaries for analysis of most medicines, therefore not representative of whole population use
Can be linked to other Australian data of interest (e.g., hospital admissions, coronial data)	Data linkage can be time consuming and costly
Longitudinal data allowing for long-term follow-up	Dose and indication for medicine use is not captured
Avoids nonresponse, attrition and reporting bias due to complete coverage	Data of dispensed medicine, therefore may not reflect medicine use or adherence

Table 5. Strength and limitations of using the Swedish Drug Register for research purposes.

Strengths	**Limitations**
Captures nationwide dispensing data	Over the counter medicines and inpatient dispensings are not captured
Longitudinal data allowing for long-term follow-up	Data of dispensed medicine, therefore may not reflect medicine use or adherence
Linked via the personal identity number to other nationwide data sources including death registry, cancer registry, social insurance, hospital admissions data	Indication for medicine use is not captured
Cost-effective compared to prospective data collection	
Avoids nonresponse, attrition and reporting bias due to complete coverage	

1.11 Aims and objectives

The overall aim of this thesis was to evaluate the patterns, predictors and outcomes of prescription opioid analgesic use. The studies in this thesis analysed general populations of people accessing prescription opioid analgesics in Australia and Sweden. The specific objectives were:

- To undertake a scoping review of the Australian published peer-reviewed literature to determine the harms and documented risk factors associated with extramedical prescription opioid analgesic use in Australia
- To determine the prevalence and incidence of prescription opioid analgesic use in Australia and compare the characteristics of people with and without cancer initiating prescription opioid analgesics
- To identify trajectories of prescription opioid analgesic use and determine predictors of persistent opioid use among people without cancer in Australia
- To determine the rate and predictors of transition to strong and high-dose opioids
- To identify trajectories of SA/DP before and after strong and weak opioid initiation for non-cancer pain in Sweden and the sociodemographic and medication-related factors associated with such trajectories

Chapter Two - Harms associated with extramedical use of prescription opioid analgesics in Australia: A scoping review

Literature to date has primarily focused on harms associated with prescription opioid analgesic use in general without differentiating between medical and extramedical use. The risk factors and harms associated with extramedical prescription opioid analgesic use may be different in nature and severity to harm resulting from use as prescribed. At the time of commencing this thesis, a review exploring the harms associated with extramedical use in Australia was not available. This chapter presents a comprehensive scoping review of the peer-reviewed literature on the harms and risk factors associated with extramedical prescription opioid analgesic use in Australia.

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Harms associated with extramedical use of prescription opioid analgesics in Australia: A scoping review

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ABSTRACT

Background: Evidence is accumulating globally on harms from extramedical prescription opioid analgesic (POA) use.
Objective: The aim of this scoping review was to explore harms and documented risk factors associated with extramedical POA use in Australia.
Methods: MEDLINE, EMBASE, PsycINFO and CINAHL were searched for original studies published between January 2000 and February 2018. Studies were eligible for inclusion if: 1) POA use was explicitly reported, 2) extramedical use was evident 3) harm was explicitly reported, 4) data were collected in/after 2000, 5) conducted in adults and 6) undertaken in Australia.
Results: We identified 560 articles and 16 met the inclusion criteria. Harms reported from extramedical POA use included: increased health service utilization (n = 5), non-fatal overdose (n = 6), fatal overdose (n = 5), injection-related injuries or diseases (n = 4), engagement in crime (n = 2), loss of employment (n = 1), and foreign body pulmonary embolization (n = 1). Multiple drug toxicity was reported as the cause of death in up to 83% of fatal overdose cases. Risk factors for harm included being male, aged 31–49 years, a history of chronic non-cancer pain, mental health disorders and/or substance abuse, and concomitant use of benzodiazepines, antidepressants or other centrally-acting substances.
Conclusion: Extramedical use of POAs is associated with a range of harms, including fatal and non-fatal overdose. Polysubstance use with other centrally-acting substances was often implicated. No published studies used linked data sources to provide a comprehensive overview of the extent of POA use or harm in Australia. Future research should focus on undertaking longitudinal cohort studies with linked data sources.

1. Introduction

Prescription opioid analgesics (POAs) alleviate pain and improve quality of life.[1,2] The role of POAs is well established in acute and chronic cancer pain but less well established in chronic non-cancer pain (CNCP).[1,3] Expansion of the opioid prescribing indications to include CNCP has contributed to increased utilization of POAs in Australia and other developed countries.[4]

Safety concerns regarding long-term POA use include adverse drug events, drug diversion and addiction.[1] Increasing prescribing of POAs has corresponded to increasing annual rates of ambulance attendances[5] and overdose deaths in the United States (US),[6] Canada[7] and Australia.[8] Opioid-related harms have now become a major public health concern,[9,10] with drug-poisoning deaths due to opioid analgesics rising in the US from 11,693 deaths in 2011[11] to 33,091 deaths in 2015.[12]

Harms from POAs have been partly attributed to the diversion of

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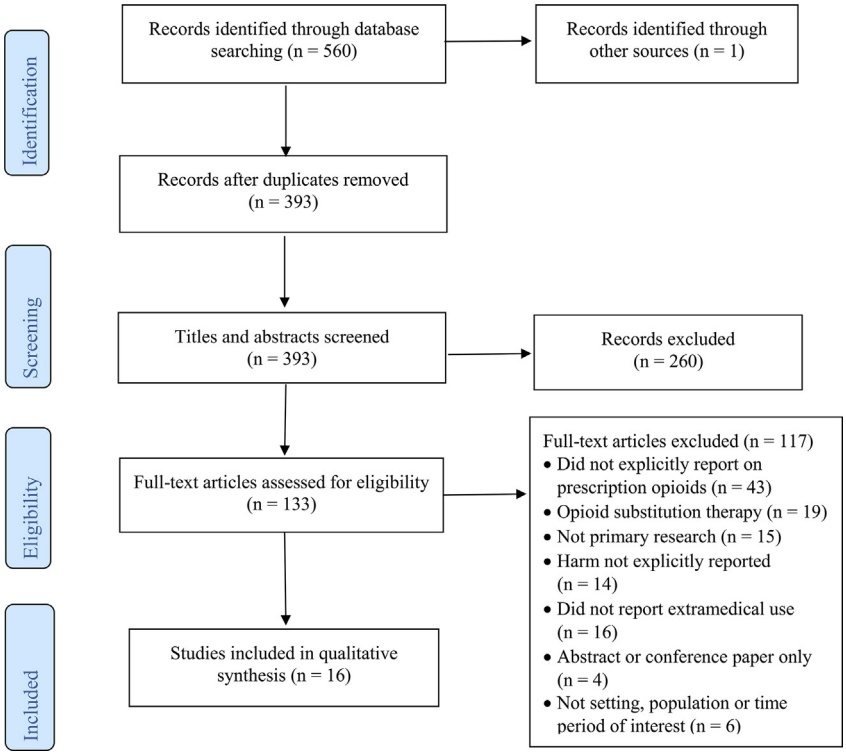

Fig. 1. PRISMA flow diagram.

prescribed opioids, including extramedical use.[13–17] Extramedical use of opioids has been widely reported internationally[18] and refers to accessing POAs outside of the formal medical system or use in a manner that is different to the prescriber's intention.[19] Extramedical use may occur among different sub-populations, including people with cancer pain, CNCP and those who use illicit drugs.[20]

POA use increased almost four-fold in Australia between 1990 and 2014,[21] however, rates of use are still lower than in the US and Canada.[4] Nevertheless, there are serious concerns that Australia is mirroring the increasing use and harm seen in the US and Canada, described as an unprecedented 'public health crisis'.[4] Emerging harm related to extramedical use of POA in Australia may be different to the US and Canada. Therefore, the aim of this scoping review was to explore harms and documented risk factors associated with the extramedical use of POAs in the Australian population.

2. Method

Scoping review methodology was used due to the anticipated heterogeneity of studies and therefore it was not possible to synthesise the results as for a systematic review.[22] In conducting a scoping review, we sought to highlight what published data exist, what data do not exist, and how this relates to opportunities for further research in Australia. Australian literature was reviewed to provide an insight into the harms and extent of extramedical use in a population that has different patterns of extramedical opioid use compared to the US and Canada (e.g. in the US non-injecting routes of POAs are common, while infrequent injecting of oral POAs is commonly reported in Australia).[23,24]

2.1. Search strategy

MEDLINE, EMBASE, PsycINFO and Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched for studies published between January 2000 and February 2018. This date range was chosen because oxycodone was listed for CNCP in 2000 and represents the most widely used strong opioid in Australia.[21] The search strategy was refined in MEDLINE and modified for subsequent databases. Subject headings and truncated terms relating to opioids, extramedical use, harm and Australia were combined. The search terms for harm were adapted from a Cochrane review examining the impact of long-term opioid use for CNCP,[25] and reflect the range of harms commonly associated with POAs including hospitalization, emergency department presentations, non-fatal and fatal overdose, and engagement in crime. See Supplement 1 for the full search strategy. We reviewed reference lists of included articles to screen for additional studies not retrieved by the initial search.

2.2. Study selection

Articles were imported into EndNote and duplicated entries removed. Titles and abstracts were screened against inclusion and exclusion criteria by two independent investigators (SL and NJ) (Fig. 1). If the relevance of the study was unclear from the title and abstract, the full text was reviewed by two investigators (SL and NJ) for possible inclusion. Any uncertainties or disagreements were resolved by discussion with a third investigator (JI).

Primary research studies were eligible for inclusion if they fulfilled the following criteria: (1) POA use was explicitly reported, (2) extramedical use was evident, (3) harms were explicitly reported, (4) data were collected during or after the year 2000, 5) conducted in adults and 6) undertaken in Australia. Studies investigating over-the-counter opioids and opioid substitution therapy (OST) were excluded.

The review was performed using the term extramedical use to describe the use of prescription opioids contrary to the prescribed instructions, including 'abuse', 'illicit use', 'problematic use', 'misuse', 'non-medical use', 'unsanctioned use' and 'extramedical use'.[19] As advocated by Larance et al., for the purpose of this review, the term extramedical use encompasses use among individuals who accessed the medication outside of the formal medical system, in addition to those whom the medications were prescribed but were used differently to the prescribed intention.[19] As extramedical use was not always explicitly stated, articles were included if they reported intentional overdose,

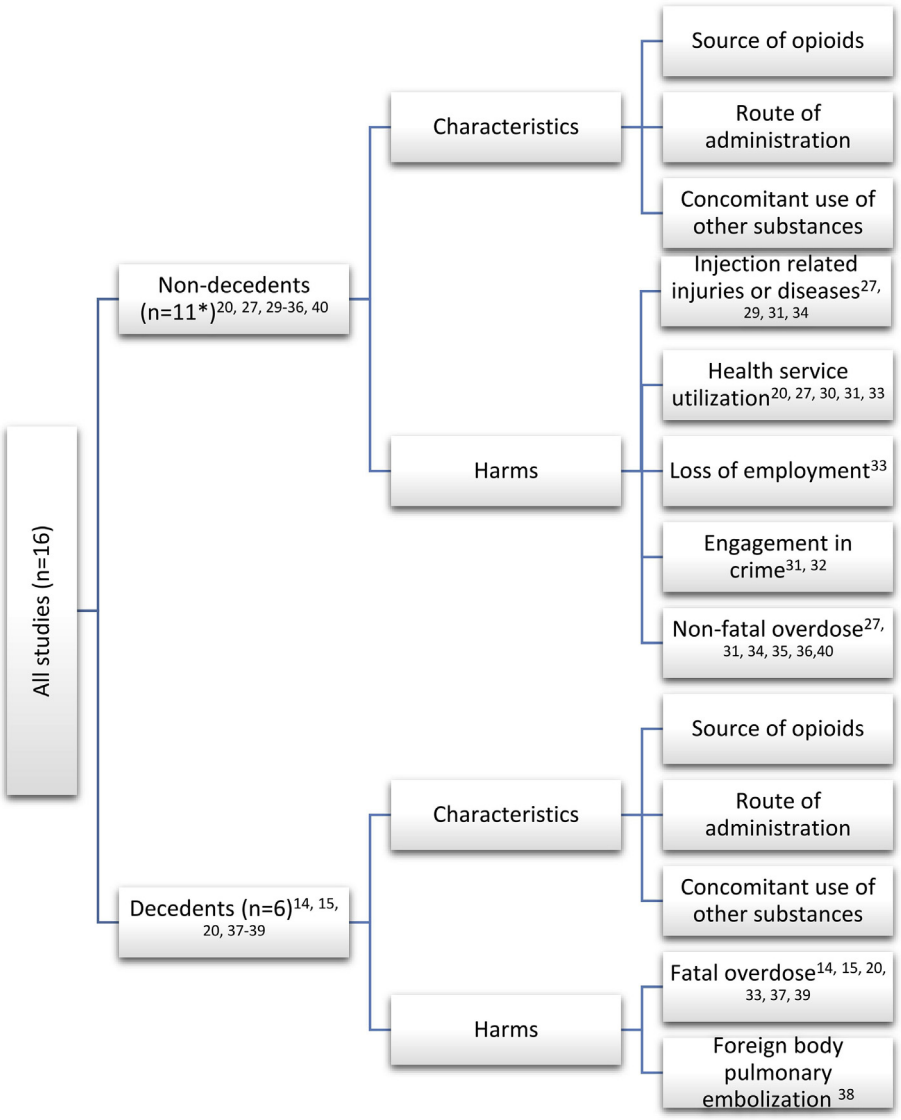

Fig. 2. Structure of results.
*One study reports on both non-decedent and decedent samples, therefore total number of studies does not add to 16.
Superscripted numbers correspond to reference numbers of articles in text.

history of drug problems or current dependence, use of an opioid via a route other than that prescribed, doctor shopping (practice of visiting multiple treatment providers to procure prescription opioids illicitly)[26,27] and obtaining opioids illicitly or from other people (e.g. family members or friends). We extracted data on harm arising from specific opioids where possible. It was often not possible to differentiate between morphine, codeine and heroin in toxicology studies because each of the opioids share common metabolites.

2.3. Data extraction and synthesis

Data extraction on author, study design, study sample, setting, data source, opioid implicated, other medications involved, extramedical use indicator, harm or service utilization were independently extracted by two investigators (SL and NJ). The results were reported according to the structure in Fig. 2.

2.4. Quality assessment

Quality assessment was conducted using the Joanna Briggs Institute (JBI) appraisal tool and checklist for prevalence studies.[28] Quality assessment was completed independently by two investigators (SL and NJ). Any differences or uncertainties between investigators were resolved by discussion with a third investigator (JI).

3. Results

A total of 560 articles were identified, of which, 16 articles satisfied our inclusion criteria (Fig. 1). Study designs included surveys of people who inject drugs (PWID) and accessed POAs outside of the formal medical system or used them differently to the prescribed intention (n = 8),[27,29–35] in-depth interviews with young people (aged 16–20) who used POAs extramedically orally or via injection (n = 1),[36] as well as retrospective audits of coronial data (n = 6)[14,15,20,37–39] and data from an injecting centre (n = 1)[40] (Table 1). There were 11 studies[20,27,29–36,40] investigating people who were alive at the time of study (non-decedent samples) and of these, seven studies were cohorts of PWID.[29–32,34,35,40] There were six studies investigating cause of death (decedent samples).[14,15,20,37–39] One study reported harm in both non-decedent and decedent samples.[20]

Extramedical use included use without a prescription (n = 6),[14,15,20,27,36,39] doctor shopping (n = 2),[15] use from an unknown

Table 1
Characteristics of included studies.

Author (Year), Study Design	Study sample (n), male %	Setting, Year of data collection	Opioid implicated, other medication involved (%)	Extramedical use indicator					Characteristics of study sample reported				
				Opioid not prescribed/ Obtained illicitly	Doctor shopping	Unknown source of opioid	History of drug and/or alcohol problems[a]	Use in a way not prescribed e.g. injection	Employment history	Enrolled in drug treatment	HCV positive	History of mental illness	History of acute/ chronic pain
Decedents													
Darke S et al. (2014), Retrospective audit	412 autopsy cases in which alprazolam was detected; 67% male	NSW, 1997–2012	Alprazolam alone or in combination with opioids in 64.6% of cases				✓		✓	✓	✓		
Darke S et al. (2015), Retrospective audit	373 autopsy cases with foreign body pulmonary embolistion; 73% male	NSW, 1997–2013	Codeine, oxycodone, fentanyl and tramadol alone or in combination with other psychotropic substances				✓		✓	✓	✓		
Darke S et al. (2011), Retrospective audit	70 autopsied cases involving oxycodone; 59% male	NSW, 1999–2008	Oxycodone with other psychotropic substances	✓			✓	✓	✓				
Pilgrim J et al. (2015), Retrospective audit and observational study	806 coronial cases of oxycodone related deaths; 59% male	Australia, 2001–2011	Oxycodone alone or in combination with other psychotropic medications	✓	✓	✓						✓	✓
Roxburgh A et al. (2013), Retrospective audit	136 coronial cases involving fentanyl; 75% male	Australia, 2000–2012	Fentanyl alone or in combination with other psychotropic substances	✓			✓	✓				✓	✓
Roxburgh A et al. (2011), Retrospective audit and observational study	465 oxycodone related deaths; 57% male	Australia, 2001–2009	Oxycodone alone or in combination with other psychotropic substances	✓			✓						✓
Non-decedents (PWID)													
Iversen J et al. (2010), Cross-sectional survey	15852 individual needle and syringe program attendees; 65% male	Australia, 1998–2008	Pharmaceutical opioids (excludes OST) alone or in combination with other psychotropic substances				✓	✓			✓		
Islam M et al. (2013), Cross-sectional survey	2395 participants who attended needle and syringe program sites; 67% male	Australia, 2011	Morphine and other opioids (excluding OST)				✓	✓		✓			

(*continued on next page*)

Table 1 (*continued*)

Author (Year), Study Design	Study sample (n), male %	Setting, Year of data collection	Opioid implicated, other medication involved (%)	Extramedical use indicator					Characteristics of study sample reported				
				Opioid not prescribed/ Obtained illicitly	Doctor shopping	Unknown source of opioid	History of drug and/or alcohol problems[a]	Use in a way not prescribed e.g. injection	Employment history	Enrolled in drug treatment	HCV positive	History of mental illness	History of acute/ chronic pain
Iversen J et al. (2017), Cross-sectional survey	1488 opioid injectors who attended needle and syringe program sites; 68% male	Australia, 2014	Prescription opioids (excluding OST) alone or in combination with other psychotropic substances (including OST)				✓	✓		✓	✓		
Degenhardt L et al. (2006), Cross-sectional survey	795 PWID (harms data available for 791); 67% male	Australia, 2004	Morphine alone or in combination with other substances including heroin	✓		✓	✓	✓	✓	✓			
Sutherland E et al. (2015), Cross-sectional survey	887 PWID; 64% male	Australia, 2013	Morphine, oxycodone alone or in combination with other psychotropic substances					✓	✓	✓			
Latimer J et al. (2016), Retrospective audit	4177 PWID; % male not reported	Sydney, 2012–2015	Fentanyl, oxycodone, morphine (use of other substances concomitantly not reported)				✓	✓					
Roxburgh A et al. (2017), Retrospective audit	8382 PWID; 75% male	Sydney, 2007–2014	Oxycodone (use of other substances concomitantly excluding heroin not reported)				✓	✓		✓			
Non-decedents													
Larance B et al. (2015), Cross-sectional survey	606 participants who regularly tamper with opioid analgesics; 69% males	Australia, 2014	'Other opioid group' including prescribed opioid analgesics (oxycodone, morphine, methadone tablets, buprenorphine patches, fentanyl, hydromorphone, dextropropoxyphene, tapentadol, tramadol, codeine)	✓	✓	✓	✓	✓	✓		✓	✓	✓
Fry R et al. (2015), Retrospective survey	44 reported completed cases of anaesthetists with substance abuse; 66% male	Australia and New Zealand, 2004–2013	Opioids including fentanyl, pethidine, morphine and oxycodone, alone or in combination with other psychotropic substances	✓				✓	✓			✓	
Dertadian G et al. (2017), Qualitative study	34 participants in total reporting extramedical use of pharmaceutical opioids; 68% male	Sydney, 2015	Pharmaceutical opioids					✓			✓		

BZDs – benzodiazepines; IRID - injection-related injuries or diseases; NOMAD – National Opioid Medications Abuse Deterrence; NSW – New South Wales; OST – opioid substitution therapy; PWID – people who inject drugs.

[a] Includes history of injection of drugs.

source (n = 5),[15,27,31,32,40] or prescription opioids obtained illicitly (n = 3).[15,27,31] Twelve studies reported on injection, snorting, chewing or any other route or method of administration not prescribed.[14,27,29–31,34–40] Twelve studies reported a history of drug and/or alcohol problems.[14,20,27,29–31,34,35,37–40] Harms are summarized in Fig. 2 and more specific details can be found in Supplement 2. Two studies[35,40] specifically investigated harm resulting from extramedical use of POAs as the primary outcome. The number of people included in the studies ranged from 34 to 15,852.[29,36]

3.1. Characteristics of non-decedent samples

Individual characteristics reported in the 11 studies conducted among non-decedent samples are summarized in Table 1 and Supplement 2. Investigating harms from extramedical use of POAs was not the primary objective of all studies and may have included people who use non-prescription opioids or do not use POAs extramedically. The proportion of males ranged from 64% to 75% and the reported mean and median age ranged from 31.8 to 40.3 years.[27,29–32] Injecting drug use was reported in seven studies[29–32,34–36] and prevalence ranged from 27% to 100%. Five studies reported being enrolled in drug treatment programs and estimates of participants enrolled ranged from 38% to 47%.[30–32,34,35] History of mental health disorders was reported by two studies,[27,33] ranging from 57% to 61% of participants. A history of drug and/or alcohol problems was reported in all studies.[20,27,29–36,40] A history of chronic pain was reported in one study.[27] Of participants who tamper with opioids (physically manipulate tablets to prepare them for unintended routes of administration),[41] 38% of people not prescribed opioids reported chronic pain or disability in the past six months compared to 80% of those who were prescribed opioids (odds ratio (OR) = 0.16 95%CI: 0.09–0.26, $p < 0.001$).[27]

3.2. Sources of opioids for non-decedent samples

Three studies reported that the source of opioid was either unknown, prescribed, not prescribed or obtained illicitly,[27,31,33] while in eight studies the source of the opioid was not reported.[20,29,30,32,34–36,40] Opioids were reported as prescribed in 71% (n = 430) of participants who tamper with opioids.[27] Additionally, 72% of participants who only tampered with prescribed opioids (n = 141) reported obtaining opioids from a medical practitioner for a medical reason.[27] One study[27] reported that people who were prescribed opioids and tamper with them reported a dealer as the source of their opioids (in 74% of people) and 'doctor shopping' as the source in 12% (n = 17) of people. Two studies reported that people used diverted opioids.[27,31]

3.3. Route of administration for non-decedent samples

Injection of opioids was reported in eight studies.[27,29–31,34–36,40] Other forms of tampering and administering oral opioid analgesics were reported in one study,[27] including past month injecting, snorting, chewing or smoking. Injection was the most commonly reported route of administration for morphine, oxycodone and fentanyl in the past month (84% of people prescribed opioids and 81% of those not prescribed the opioids).[27] Snorting, chewing or smoking were the most common routes of administration for codeine (5% of people prescribed opioids and 8% of those not prescribed the opioids).[27] Iversen et al.[29] reported that 8% of a cohort of PWID (n = 15,852) last injected a pharmaceutical opioid.

3.4. Concomitant use of other substances for non-decedent samples

Concomitant psychotropic drug use was reported in six studies[27,31–33,35,36] (Table 2), with prior or concomitant benzodiazepine use reported in two studies.[27,31] One study[31] reported that people who inject morphine are four and a half times more likely to inject multiple drugs compared to people who inject heroin (95% CI 3.48–6.04).

3.5. Harms among non-decedent samples

3.5.1. Injection related injury or disease (IRID)

Four studies reported IRID related to extramedical use of opioids.[27,29,31,34] Two studies reported HCV antibody presence in PWID[29,34] and two studies reported other injection-related harms.[27,31] Iversen et al.[29] reported that females with a short history of injecting (≤4 years) who used opioids as the last drug injected had more than double the odds of testing HCV antibody positive compared to those who last injected methamphetamine, whilst males had an OR of 1.77 (95% CI 1.03–3.04). In two studies,[27,31] up to 77% of people with recent opioid injection reported IRID. Degenhardt et al.[31] reported that swelling of arm and/or hand (46%, n = 199), difficulty finding veins into which to inject (36%, n = 130) and scarring/bruising (27%, n = 97) were commonly reported IRID among people who inject morphine. IRID of any severity was similar (71% vs. 63%) for those who tamper with prescribed opioids and those who did not have the opioid prescribed.[27]

3.5.2. Health service utilization

Five studies reported utilization of a health service due to extramedical POA use.[20,27,30,31,33] Roxburgh et al.[20] reported that outpatient treatment episodes for problematic oxycodone use doubled (0.01–0.02 per 1000 population) from 2002-03 to 2007–08, while hospitalization due to poisoning with morphine, oxycodone and codeine also doubled (0.05–0.11 per 1000 population) from 1999-2000 to 2007–08. Islam et al.[30] reported that of participants reporting morphine and other opioids (excluding OST) as the drug injected most recently, 16% (n = 51) accessed a hospital emergency department, however, there was no correlation between opioid injected and emergency department visit (OR = 1.18 95% CI (0.80–1.74).

3.5.3. Loss of employment

One study[33] surveyed the heads of accredited anaesthesia departments across Australia to examine substance abuse among registered anaesthetists. This was defined as 'an anaesthetist who had come to the attention of the department as a result of suspected substance abuse and required some form of intervention'.[33] Of 44 cases of substance abuse which provided detailed reports, 14 anaesthetists were using opioids extramedically.[33] Only one third (36%) of those using opioids extramedically continued to work in anaesthesia.[33]

3.5.4. Engagement in crime

Two studies[31,32] reported that engagement in crime or being arrested were more common among participants who used POAs extramedically compared to those that do not use opioids extramedically but use other substances. Of PWID, those who had recently committed a property crime had 50% higher odds to report illicit oxycodone use than those that did not commit a property crime.[32]

3.5.5. Non-fatal overdose

Non-fatal overdose from POAs was reported in six of 11 studies.[27,31,34–36,40] Larance et al.[27] reported that of 141 people who were using prescribed opioids extramedically, 9% (n = 13) reported experiencing an overdose in the past year. Degenhardt et al.[31] reported that the rate of lifetime morphine overdose was relatively low compared to heroin overdose in people who recently injected morphine (6% vs. 56%). Dertadian et al.[36] reported that 42% (n = 5) of individuals using POAs reported personal experience of an overdose. In contrast, none of the individuals using extramedical POAs via the oral route reported any

Table 2
Concomitant medication use.

Author (Year)	Opioid reported	How was role of opioid defined	Source of opioid	Concomitant use of other psychoactive substance
Decedents				
Darke S et al. (2014)	Oxycodone, codeine, tramadol, dextropropoxyphene	Opioid related death was not the primary outcome. Toxicological data was reported for opioids.	Not reported	· Alprazolam was reported in all cases (primary outcome), other psychoactive substances were not explicitly reported with opioids.
Darke S et al. (2015)	Oxycodone, codeine, fentanyl, tramadol	Opioid related death was not the primary outcome. Toxicological data was reported for opioids.	Not reported	· Multiple psychoactive substances were present in 91.2% of cases. These were not explicitly reported in regards to concomitant use with opioids (not primary outcome of study).
Darke S et al. (2011)	Oxycodone	Cause of death attributed to oxycodone toxicity or the acute physical sequelae of such toxicity. Role of oxycodone toxicity was determined with reference to known toxic concentrations.	· 70% had oxycodone prescribed to them for chronic pain · 30% did not have oxycodone prescribed to them	· All cases had other substances detected · 54.3% had other opioids present (including heroin) · 68.6% had BZDs or zolpidem · 41.4% had antidepressants present · 18.6% had antipsychotics present · 32.9% had alcohol present · 7.1% had psychostimulants (e.g. methamphetamines) present
Pilgrim J et al. (2015)	Oxycodone	All deaths where oxycodone was detected including oxycodone monotoxicty, combined drug toxicity, natural disease, external injuries and undetermined causes.	· 39% had legitimate prescription for oxycodone, of whom 4% had been defined as 'doctor shopping' for oxycodone · Majority (no number specified) of cases where oxycodone was prescribed involved non-cancer chronic pain, of which back pain was the most common (30%) · 8% of prescriptions were provided for cancer management · 61% either did not involve a prescription or this information was not available in the coroners reports, of whom 5% involved oxycodone sourced from various places *NB: 74.4% of cases involved minor to no description on the drugs in the coroner's finding*	· Not specified which ones were commonly found in combination but states that 63.4% involved multiple or combined drug toxicity as cause
Roxburgh A et al. (2013)	Fentanyl	Fentanyl toxicity was determined by a coroner to be the underlying, or contributory cause of the death.	· 36% had a recorded history of prescribed fentanyl at the time of death	· 66% had other drugs present in addition to fentanyl at the time of death · 45% had BZDs present · 18% had morphine present in toxicology (likely heroin) · 16% had oxycodone present · 26% had antidepressant present · 15% had amphetamines present · 7% had cannabis present
Roxburgh A et al. (2011)	Oxycodone	Oxycodone toxicity or overdose was recorded as a direct or contributory cause of death and where oxycodone was found at fatal levels in the blood.	· 53% had a recorded history of prescribed oxycodone at the time of death	· Multiple drug toxicity was predominant (82% of deaths) with BZDs and alcohol commonly implicated in death (no specific numbers reported and no break down available of other substances)
Non-decedents (PWID)				
Iversen J et al. (2010)			Not reported	· No information on concomitant use

(*continued on next page*)

Table 2 (*continued*)

Author (Year)	Opioid reported	How was role of opioid defined	Source of opioid	Concomitant use of other psychoactive substance
	Pharmaceutical opioids (excludes OST). No specific definition.	Reported pharmaceutical opioids as the drug last injected.		· No information on concomitant use · No information on concomitant use
Islam M et al. (2013)	Morphine and other opioids (excluding OST). No specific definition.	Reported morphine/other opioids as the drug injected most recently.	Not reported	
	Iversen J et al. (2017), Cross-sectional survey	Prescription opioids (excluding OST) alone or in combination with other psychoactive substances (including OST)	Reported injection of prescription opioids in the previous six months.	
	Not reported			
Degenhardt et al. (2006)	Morphine	Reported injecting morphine recently.	· Obtained morphine illicitly (not prescribed to the participants)	· 19% of the recent morphine injectors group injected BZDs in the past six months · 71% used alcohol in the past six months
Sutherland E et al. (2015)	Morphine, oxycodone	Illicit use of oxycodone and morphine reported (no further detail).	· Illicit use with no further detail of source of opioid	· 32% reported being under the influence of two substances · 12% reported being under the influence of more than two substances at the time of last offence (no information about what substances)
Latimer J et al. (2016)	Fentanyl, oxycodone, morphine	Drug injected is self-reported post overdose to clinical staff.	Not reported	Not reported · If deemed intoxicated on presentation to use the service, they were excluded and asked to re-present at a later time.
Roxburgh A et al. (2017)	Oxycodone	Drug injected is self-reported.	Not reported	· 51% of people who overdosed on oxycodone overdosed on both heroin and oxycodone · 8% of people who overdosed on oxycodone were receiving methadone
Non-decedents				
Larance B et al. (2015)	People who regularly tamper with opioid analgesics	Reported chewing, snorting, smoking and/or injecting opioid medication. The 'other opioid group' included prescription opioid analgesics.	· Those in 'other opioids group' had been prescribed at least one opioid analgesic, but could have additionally used diverted pharmaceutical opioids	· 75% of 'other opioids only group' used BZDs on 15 (range 1–28) median days in the past month · 64% of 'not prescribed group' used BZDs on 5 (1–28) median days in the past month
Fry R et al. (2015)	Opioids (fentanyl, pethidine, morphine and oxycodone)	Suspected opioid abuse.	Not reported	· Polysubstance abuse was noted in 25% of cases, with 91% of opioid cases commonly involved in polysubstance abuse
Dertadian G et al. (2017), Qualitative study	Pharmaceutical opioids. No specific definition.	Reported nonmedical use of pharmaceutical opioids and used at least twice in the past 90 days. Sometimes role of opioid was unclear.	· Participants reporting extramedical use of oral pharmaceutical opioid, the source of opioid was through leftover prescriptions, friendship networks and internet. · Minimal detail on source of pharmaceutical opioid for the participants using opioids intravenously. However, 67% had been exposed to pharmaceutical opioids in a medical setting prior to extramedical use.	· Polysubstance abuse was reported with no specific detail

BZDs – Benzodiazepines; OST – opioid substitution therapy.

first-hand experience of overdoses.[36] Latimer et al.[40] reported that of those injecting fentanyl extracted from transdermal patches (n = 2454) at the Sydney Medically Supervised Injecting Centre, 4% (n = 98) were followed by a subsequent overdose, compared with 2% of heroin injections. Roxburgh et al.[35] reported that of 909 people who experienced overdose at the Sydney Medically Supervised Injecting Centre, 34% overdosed on oxycodone.

3.6. Characteristics of decedent samples

Individual characteristics reported in the six coronial studies conducted among decedent samples are summarized in Table 1 and Supplement 2. Harms from extramedical use of POAs were not the primary objective of these studies and may have included people who use non-prescription opioids or do not use POAs extramedically. Across studies, the proportion of decedents who were male ranged from 57% to 75% and the reported mean age ranged from 39 to 48.9 years.[14,20,39] A history of injecting drug use was evident in four studies involving fatal overdose,[14,20,37,39] and the percentage of people with injecting drug use history ranged from 27% to 80%. History of a mental health disorder was reported by three studies,[15,33,39] with the percentage of individuals ranging from 44% to 57%. Roxburgh et al.[39] reported a significant difference in recorded mental health disorders between those who have an injecting drug use history compared to those with no injecting drug use history (39% vs 61%, $p < 0.05$). Two coronial studies[20,39] reported that PWID were significantly more likely to be male and younger than non-PWID and have a recorded history of drug dependence. Risk factors for overdose in PWID vs non-PWID are reported in Supplement 3 for specific opioids.

3.7. Sources of opioids and indication for opioid use prior to death

Four studies reported the proportion of individuals who were prescribed the opioid involved in the fatal overdose, ranging from 36% to 70% of coronial cases.[14,15,20,39] A prescription for the decedent was not involved or this information was not available for remaining cases. Pilgrim et al.[15] reported that among the 39% of 806 cases involving a legitimate prescription of oxycodone, 4% of individuals were identified to be 'doctor shopping'. Oxycodone was sourced from relatives, friends or a spouse in 5% (n = 24) of cases that did not have a legitimate prescription (n = 494).[15] One study reporting fentanyl-related deaths (n = 136) identified that 7% of decedents were health professionals who had access to controlled opioid medication.[39]

Indication for the opioid prescribed was reported in only one study,[15] with the most common indication being CNCP.[15] Pilgrim et al.[15] reported that for decedents who were using opioids extramedically, most individuals were intending to achieve pain relief rather than to seek a 'high'. Three coronial studies[14,20,39] reported that opioid-related deaths among non-PWID were more likely to have a recorded history of chronic pain compared to PWID. History of recorded acute or chronic pain ranged from 37% to 46% of fatal overdose cases.[15,39]

3.8. Route of administration prior to death

Injection of POAs was reported in two fatal overdose studies[14,39] and one study investigating foreign body pulmonary embolization.[38] Darke et al.[14] reported 21% of cases injected oxycodone prior to death and that injection was less likely among women than men (OR = 0.16, 95%CI: 0.03–0.76). Roxburgh et al.[39] reported 51% of cases injected fentanyl at the time of overdose.

3.9. Concomitant use of other substances prior to death

Concomitant use of opioids with other substances was reported in all of the studies[14,15,20,33,37,39] (Table 2). Quantitative estimates of concomitant psychotropic drug use ranged from 63% to 100%.[14,15,20,33,39] Concomitant use of benzodiazepines or antidepressants ranged from 45% to 69% and 26%–41%, respectively.[14,39] Reported concomitant alcohol use ranged from 17% to 33%.[14,39]

3.10. Harms among decedent samples

3.10.1. Fatal overdose

Six studies reported fatal overdose from extramedical use of POAs,[14,15,20,33,37,39] while one descriptive study investigated foreign body pulmonary embolization as the primary outcome.[38]. One study[37] focused on alprazolam-related deaths, with opioids detected in 65% (n = 266) of cases. Presence of opioids was highest (89%) in accidental drug overdoses involving alprazolam.[37] One study[33] reporting on patterns of substance abuse in anaesthetists identified two cases of death due to opioid abuse. Death due to multiple drug toxicity was reported in all studies,[14,15,20,33,37,39] with multiple drug toxicity being the most common cause of death in up to 83% of fatal overdose cases. A relationship between opioid injection and foreign body pulmonary embolization was not examined.

4. Methodological quality of included studies

The quality assessment of all studies is summarized in Supplement 4. Twelve studies[14,15,20,27,29–32,34,35,39,40] used a sample frame appropriate to address the target population of people who use POA. The setting and characteristics of the study participants who use POAs were described in detail in eight studies.[14,15,20,27,31,34,36,39] The coronial audit studies[14,15,20,37–39] assessed outcome (death) based on existing diagnostic criteria. Participants for six survey studies[27,29–32,34] were recruited through a variety of settings including needle-syringe programs, snowballing and word of mouth, drug treatment services, community pharmacies, advertisements in newspapers and street media. It was unclear whether the response rate for these studies was adequate and if not, whether the low response rate was managed appropriately. Additionally, the difference between respondents and non-respondents was not discussed, presumably due to the difficulty given the variety of recruitment methods. Reimbursement of participants was reported in three studies.[31,32,36]

5. Discussion

To our knowledge, this is the first comprehensive review of risk factors and harms associated with extramedical use of POAs in Australia. This review confirms that harms associated with extramedical use of POAs in Australia are similar to that evident in the US and Canada. However, this review also highlights that Australia is in a unique position to avoid the scale of harm seen elsewhere. Extramedical use was associated with a range of harms, of which fatal and non-fatal overdose were most common. Overdoses often occurred in persons with multiple drug toxicity and a history of mental health disorders or substance misuse. This suggests that comprehensive multifactorial strategies to reduce harm that address the social, clinical and economic determinants of extramedical use are likely to be more effective than strategies that target opioid use alone. In addition, we identified key gaps in the published literature. These gaps included a lack of longitudinal population-based studies and a lack of studies that describe direct causal mechanisms via which extramedical use of specific opioids result in harm.

Complex patterns of polysubstance use were identified across all studies, with up to 68% of fatal overdoses involving concomitant use of POAs and benzodiazepines. Although attributing rates of harm to specific POAs is difficult when polysubstance use is present, our findings highlight the need for greater vigilance when prescribing POAs and psychotropic medications, particularly benzodiazepines, antidepressants and other centrally-acting substances. Similarly, Cochran et al.[42] reported that people with mental health disorders had the

highest odds for opioid misuse assessed using a 6-item Prescription Opioid Misuse Index. Three studies included in our review reported the prevalence of mental health disorders without defining the nature of these disorders.[15,33,39] Therefore, it was not possible to determine whether specific mental health disorders are associated with increased risk of extramedical use of POA. However, high rates of polysubstance use and mental health comorbidity suggest that strategies to reduce harm should be implemented broadly through health and community services.

Our review highlights that there are two main Australian sub-populations where extramedical use of POAs occurs. The first is among people without a history of drug abuse who access POAs mainly for CNCP. The second is among individuals already dependent on illicit opioids or other substances. PWID were more likely to be male, younger and have a recorded history of drug dependence than those not injecting drugs. History of acute or chronic pain was found to be higher in those with no injecting drug use history compared to PWID. Additionally, Pilgrim et al.[15] reported that of people who used oxycodone extramedically prior to death, most intended to achieve better pain relief of CNCP rather than seek a 'high'. This suggests that extramedical use of POAs in individuals with CNCP may arise due to suboptimal pain management, including inappropriate opioid analgesic prescribing.

The studies included in our review used a diverse range of data sources. No single data source permitted a comprehensive evaluation of the true extent of extramedical POA use or harms. Importantly, the majority of the studies did not investigate extramedical POA use and harm as their primary objective. Inconsistencies in the definitions or reporting of extramedical POA use, the types of prescription opioids considered, use of other substances, and the presence of chronic pain and mental health disorders limit comparability between studies. No study combined data from multiple sources, although data linkage of prescription-based datasets to health and social outcomes presents an avenue to explore into the future. However, defining extramedical POA use in Australian administrative pharmacy data has proved challenging.[43] A purposefully designed cohort study of people who use POAs extramedically linked to various data sources would provide more comprehensive data on harms associated with POA use.

Currently in Australia, it is not known whether the risk of harms varies across different time points after extramedical use of POAs commences or across all opioids, particularly between strong (e.g. oxycodone, fentanyl) and weaker (e.g. codeine, tramadol) opioids. Importantly, this review has highlighted that extramedical use may occur across all groups of people using opioids, including among those without a history of drug abuse. Hence, future studies investigating harm from extramedical POA use need to assess all harm related to opioid use in people with and without a history of drug dependence.

Existing monitoring systems cannot identify and track opioid prescriptions at the individual patient level at the time of prescribing. The real-time prescription drug monitoring program (PDMP) in Tasmania and Victoria will assist in providing more information,[44] however, it is currently not an Australia-wide initiative and is voluntary. A PDMP in Florida has been successful at reducing oxycodone-related mortality.[45] However, PDMPs alone will not provide information on the complex range of social, clinical and economic determinants of extramedical POA use. PDMPs aim to enable medical practitioners and pharmacists to identify people whose dispensing pattern of opioid prescriptions is suggestive of potential extramedical use and therefore at risk of harms. However, inappropriate opioid prescribing may also contribute to extramedical use and this may not be captured by the program. Additionally, the program will only target specific 'high risk' medication and therefore may not capture all problematic substance use. Surveys focusing on PWID are not representative of the general population[31] and therefore, have reduced capacity to identify possible extramedical use among people with CNCP. There needs to be a balance between restricting use of POAs to reduce abuse potential vs maintaining adequate access to those who require opioids for appropriate pain management.

5.1. Strength and limitations

A key strength of this review is the comprehensive search of published peer-reviewed literature. The scoping review methodology provided the opportunity to include research utilizing heterogeneous study designs. However, as grey literature was not included there remains the possibility that some relevant research was not considered.

Although the JBI critical appraisal tool does not consider self-report as a valid method for assessment of the outcome,[46] we deemed self-report as an appropriate method for assessing medication use in the PWID population given the challenges in studying this population.[47] Few studies in this review identified reasons for extramedical use and the heterogeneity of the reported study methods and designs made synthesis of data difficult. Due to the population characteristics where polysubstance use is common, it was challenging to assess how extramedical use of POAs in isolation impacted on harms. Additionally, extramedical use was often difficult to separate from appropriate use of POAs and therefore, some of the results may not be a direct consequence of extramedical use.

6. Conclusion

Extramedical use of POAs in Australia has been associated with a range of harms, including fatal and non-fatal overdose. Specific risk factors for harms included being male, aged between 30 and 49 years, having a history of CNCP, mental health disorders, and/or substance abuse, and concomitant use of benzodiazepines, antidepressants or other centrally-acting substances. No published studies linked data from multiple sources to provide a comprehensive overview of the extent of extramedical POA use in Australia. Linking administrative datasets may provide new opportunities for longitudinal research into the extent and harms associated with extramedical POA use.

Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sapharm.2018.07.001.

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Appendix A. Search strategy

MEDLINE

1 Analgesics, Opioid/

2 pharmaceutical opioid$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3 Narcotics/

4 Buprenorphine/

5 Codeine/

6 Fentanyl/

7 Hydrocodone/

8 Methadone/

9 Dextropropoxyphene/

10 Morphine/

11 Oxycodone/

12 Meperidine/

13 pethidine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14 tapentadol.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

15 Tramadol/

16 (narcotic? or opiate$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17 opioid$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

18 Opium/

19 Hydromorphone/

20 dihydrocodeine.mp.

21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22 (abberant adj behavio?r).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

23 (abuse? and (drug? or opioid$ or substance? or sedative? or hypnotic?)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

24 abuse liability.mp.

25 (addict$ and (drug? or opioid$ or substance? or sedative?)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

26 Behavior, Addictive/

27 Crime/

28 Dangerous Behavior/

29 (depend$ and (drug? or opioid$ or substance? or physical or sedative? or hypnotic?)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

30 Prescription Drug Diversion/

31 diversion?.mp.

32 Morphine Dependence/ or dependence.mp.

33 doctor shopping.mp.

34 Drug Users/

35 NMUPD.mp.

36 Prescription Drug Misuse/

37 Drug-Seeking Behavior/

38 "excessive use".mp.

39 "non-prescribed use".mp.

40 Habits/

41 hazardous use?.mp.

42 heavy use?.mp.

43 illegal use?.mp.

44 illicit use?.mp.

45 intoxication?.mp.

46 misuse?.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

47 mis-use.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

48 overuse.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

49 "non-prescription use?".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

50 "problem use".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

51 Opioid-Related Disorders/

52 "psychoactive effect?".mp.

53 Risk-Taking/

54 Street Drugs/

55 Substance-Related Disorders/

56 substance abuse.mp.

57 chemical dependenc$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

58 pharmaceutical misuse.mp.

59 injectable drug?.mp.

60 Substance Abuse, Intravenous/ or "injection drug use".mp.

61 (manipulat$ adj behavio?r).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

62 (snort$ or crus$ or "skin pop$" or "rectal stuffing" or "vaginal stuffing" or "body stuffing").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

63 drug abuse.mp.

64 'nonmedical use'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

65 Death/

66 Asphyxia/

67 harm.mp.

68 Brain Death/

69 Death/

70 Death, Sudden/

71 Death, Sudden, Cardiac/

72 Drowning/

73 excess dose?.mp.

74 Fatal Outcome/

75 Mortality, Premature/ or Hospital Mortality/ or Mortality/

76 non-fatal$.mp.

77 nonfatal$.mp.

78 Drug Overdose/

79 opiate overdose.mp.

80 opioid$ overdose.mp.

81 pharmac$ poison$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

82 Poisoning/

83 Drug-Induced Liver Injury/

84 "Drug-Related Side Effects and Adverse Reactions"/

85 Hospitalization/

86 hospitalisation.mp.

87 acute admission?.mp.

88 ER visit?.mp.

89 ED visit?.mp.

90 Emergency Service, Hospital/ or Emergency Medical Services/ or Emergency Services, Psychiatric/

91 emergency room visit?.mp.

92 emergency visit?.mp.

93 Critical Care/

94 Emergencies/

95 Emergency Treatment/

96 Poison Control Centers/

97 emergency admission.mp.

98 Suicide/

99 suicide?.mp.

100 respiratory depression.mp. or Respiratory Insufficiency/

101 central nervous system depression.mp.

102 CNS depression.mp.

103 Morbidity/

104 'extra medical use'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

105 22 or 23 or 24 or 25 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 104

106 26 or 27 or 28 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103

107 Australia/

108 'opioid use'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

109 Drug Utilization/

110 Infection/

111 105 or 108 or 109

112 106 or 110

113 Chronic Disease/

114 (wounds and injuries).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

115 Contusions/

116 Hip Dislocation/ or Fracture Dislocation/ or Shoulder Dislocation/ or Hip Dislocation, Congenital/

117 Spinal Fractures/ or Fractures, Compression/ or Femoral Neck Fractures/ or Radius Fractures/ or Tibial Fractures/ or Femoral Fractures/ or Rib Fractures/ or Ankle Fractures/ or Humeral Fractures/ or Fractures, Avulsion/ or Hip Fractures/ or Skull Fractures/ or Mandibular Fractures/ or Osteoporotic Fractures/ or Fractures, Open/ or Fractures, Bone/ or Ulna Fractures/ or Shoulder Fractures/ or Fractures, Stress/ or Fractures, Closed/

118 Hand Injuries/

119 Multiple Trauma/

120 Soft Tissue Injuries/

121 (sprains and strains).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

122 Tendon Injuries/

123 Accidents, Traffic/

124 "Wounds and Injuries"/ or motor vehicle accidents.mp.

125 Accidental Falls/

126 Trauma, Nervous System/

127 Postural Balance/

128 Bone Density/

129 Arm Injuries/

130 Lacerations/

131 Soft Tissue Injuries/

132 Bone Diseases, Metabolic/

133 slip$.mp.

134 stumbl$.mp.

135 trip$.mp.

136 tumbl$.mp.

137 fall$.mp.

138 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137

139 21 and 107 and 111 and 138

140 limit 139 to yr="2000 -Current"

EMBASE

1 opiate/

2 narcotic agent/

3 buprenorphine/

4 codeine/

5 fentanyl/

6 hydrocodone/

7 hydromorphone/

8 methadone/

9 dextropropoxyphene/

10 morphine/

11 oxycodone/

12 pethidine/

13 meperidine.mp.

14 tapentadol/

15 tramadol/

16 opioid.mp.

17 narcotic analgesic agent/

18 drug abuse/ or drug misuse/ or substance abuse/ or misuse.mp.

19 drug dependence/

20 prescription drug diversion/

21 doctor shopping.mp.

22 drug seeking behavior/ or opiate addiction/

23 'excessive use'.mp.

24 'heavy use'.mp.

25 'illegal use'.mp.

26 'illicit use'.mp.

27 intravenous drug abuse/

28 street drug/

29 'nonmedical use'.mp.

30 'non-medical use'.mp.

31 'non-prescription use'.mp.

32 'overuse'.mp.

33 drug intoxication/

34 addictive behavior.mp.

35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36 drug overdose/

37 brain death/ or sudden cardiac death/ or death/ or sudden death/

38 asphyxia/

39 harm.mp. or patient harm/

40 drowning/

41 excess dose?.mp.

42 fatal outcome.mp. or fatality/

43 hospital mortality.mp. or mortality/

44 non-fatal$.mp.

45 poisoning.mp. or intoxication/

46 toxic hepatitis/

47 hospitalization/

48 health care utilization/ or emergency health service/ or emergency ward/ or ER visit.mp. or hospital admission/

49 emergency treatment/

50 emergency/

51 critical care.mp. or intensive care/

52 central nervous system depression/

53 CNS depression.mp.

54 respiratory insufficiency.mp. or respiratory failure/

55 respiration depression/

56 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55

57 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

58 Australia/

59 'opioid use'.mp.

60 infection/

61 35 or 59

62 56 or 60

63 falling/

64 fall$.mp.

65 soft tissue injury/

66 humeral head fracture/ or humerus fracture/ or fracture dislocation/ or leg fracture/ or compression fracture/ or proximal fibula fracture/ or fibula fracture/ or femur shaft fracture/ or orbit fracture/ or humeral neck fracture/ or nose fracture/ or wrist fracture/ or skull base fracture/ or fracture.mp. or fracture/ or proximal radius fracture/ or distal tibia fracture/ or hip fracture/ or jaw fracture/ or elbow fracture/ or limb fracture/ or foot fracture/ or scapula fracture/ or proximal humerus fracture/ or joint fracture/ or finger fracture/ or scaphoid fracture/ or radius head fracture/ or maxilla fracture/ or tibia fracture/ or multiple fracture/ or femoral head fracture/ or femur intertrochanteric fracture/ or shoulder fracture/ or ulna fracture/ or cartilage fracture/ or face fracture/ or proximal femur fracture/ or forearm fracture/ or fibula shaft fracture/ or arm fracture/ or spine fracture/ or avulsion fracture/ or femur subtrochanteric fracture/ or ankle fracture/ or tibia shaft fracture/ or fracture immobilization/ or hand fracture/ or femur fracture/ or tibial plateau fracture/ or distal femur fracture/ or radius fracture/ or fracture healing/ or proximal tibia fracture/ or skull fracture/ or fracture external fixation/ or open fracture/ or acetabulum fracture/ or pelvis fracture/ or fracture fixation/ or femoral neck fracture/ or radius shaft fracture/ or knee fracture/ or catheter fracture/ or metacarpal bone fracture/ or distal radius fracture/ or rib fracture/ or mandible fracture/ or distal fibula fracture/ or patella fracture/ or clavicle fracture/ or intraarticular fracture/ or malleolus fracture/ or closed fracture reduction/

67 tendon injury/

68 laceration/

69 arm injury/

70 (wounds and injuries).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

71 bone density/

72 slip$.mp.

73 stumbl$.mp.

74 trip$.mp.

75 tumbl$.mp.

76 body equilibrium/

77 motor vehicle accident.mp. or traffic accident/

78 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77

79 57 and 58 and 61 and 78

80 limit 79 to yr="2000 -Current"

PsychINFO

1 Opiates/

2 MORPHINE/

3 oxycodone.mp.

4 FENTANYL/

5 BUPRENORPHINE/

6 METHADONE/

7 CODEINE/

8 hydromorphone.mp.

9 hydrocodone.mp.

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11 Drug Abuse/

12 'opioid use'.mp.

13 Drug Abuse Liability/ or Drug Dependency/ or Drug Addiction/ or Prescription Drugs/ or Drug Usage/

14 Suicide/ or harm.mp.

15 HOSPITALIZATION/

16 "Death and Dying"/

17 CRIME/

18 Infectious Disorders/

19 ADDICTION/

20 Respiratory Distress/ or Drug Overdoses/ or respiratory depression.mp.

21 nonfatal overdose.mp.

22 Health Care Utilization/ or Emergency Services/

23 poison control center.mp.

24 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25 Drug Usage/

26 11 or 12 or 13 or 25

27 australia.mp.

28 fall$.mp. or FALLS/

29 Head Injuries/ or Injuries/ or Motor Vehicles/ or soft tissue injuries.mp. or Transportation Accidents/

30 fracture.mp.

31 Bone Disorders/ or Osteoporosis/ or Bones/

32 Motor Coordination/ or Equilibrium/

33 Motor Traffic Accidents/ or Trauma/

34 24 or 28 or 29 or 30 or 31 or 32 or 33

35 10 AND 26 AND 27 AND 34

36 limit 35 to yr="2000 -Current

CINHAL

(opioid OR opiate OR oxycodone OR codeine OR buprenorphine OR morphine OR fentanyl OR hydrocodone OR methadone OR meperidine OR tapentadol OR tramadol OR hydromorphone OR dextropropoxyphene) AND (harm OR hospitalisation OR infection OR drug overdose OR mortality OR crime OR emergency OR death OR asphyxia OR opioid overdose OR fall OR fracture OR motor vehicle accident) AND (misuse OR opioid use OR abuse OR nonmedical use OR extramedical use OR non-prescribed use) AND (Australia)

Chapter Three - Prevalence and incidence of prescription opioid analgesic use in Australia

The scoping review in Chapter Two identified that extramedical use of prescription opioid analgesics is associated with serious harms in Australia. The harms are similar to those evident in the US and Canada, however Australia has not yet reached the scale of harm seen there. The review identified that it was often difficult to delineate extramedical prescription opioid analgesic use from use as prescribed. Additionally, the review identified that initiation of opioids for CNCP may result in extramedical prescription opioid analgesic use if pain control is inadequate because people may increase doses without their prescriber's knowledge with the aim of reducing pain. This is an important finding as it provokes investigation into opioid prescribing and the patterns of use that may provide signals for extramedical use and consequent harm.

The CDC has identified three 'problematic' patterns of opioid use that are associated with increased risk of harm. One of the target areas is to reduce excess opioid prescribing. Opioid use in the US appears to have started to decline in recent years, since the peak in 2012. The prevalence and incidence of prescription opioid analgesic use in Australia in recent years has not been investigated. This chapter explores the rates of opioid use and the characteristics of people with and without cancer initiating opioids in Australia.

Poisson regression was used in this chapter to determine the rate ratios for the prevalence and incidence of prescription opioid analgesic use. To compare the characteristics of people with and without cancer, Pearson's chi-square test was used to compare proportions for categorical variables, and Student's t-test was used for continuous variables. Some of the risk factors for extramedical use that were identified in the scoping review in Chapter Two, including benzodiazepine use, age and gender, were investigated in people with and without cancer initiating opioids.

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ORIGINAL ARTICLE

Prevalence and incidence of prescription opioid analgesic use in Australia

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Keywords Australia, drug utilization, incidence, pain, prevalence, opioid analgesics

AIMS

The aims of the current study were to determine the prevalence and incidence of prescription opioid analgesic use in Australia and compare the characteristics of people with and without cancer initiating prescription opioid analgesics.

METHODS

A retrospective population-based study was conducted using the random 10% sample of adults who were dispensed prescription opioid analgesics in Australia between July 2013 and June 2017 through the Pharmaceutical Benefits Scheme. Poisson regression was used to calculate rate ratios (RR) for opioid prevalence and incidence. The characteristics of people initiating opioids, including type of opioid initiated, total oral morphine equivalents dispensed, prescriber speciality, medical comorbidities, and past analgesic and benzodiazepine use, were compared for people with and without cancer.

RESULTS

Opioid prevalence increased {RR = 1.006 [95% confidence interval (CI) 1.004, 1.008]}, while incidence decreased [RR = 0.977 (95% CI 0.975,0.979)] from 2013/2014 to 2016/2017. There were between 287 677 and 307 772 prevalent users each year. In total, 769 334 adults initiated opioids between 2013/2014 and 2016/2017, and half of these initiations were by general practitioners. Initiation with a strong opioid occurred in 55.8% of those with cancer and 28.2% of those without cancer.

CONCLUSION

Rates of opioid use have remained high since 2013, with approximately 3 million adults using opioids and over 1.9 million adults initiating opioids each year. Between 2013 and 2017, opioid prevalence has slightly increased but incidence has decreased. People without cancer account for the majority of opioid use and are more likely to be initiated on short-acting and weak opioids. Initiation of strong opioids has increased over time, reinforcing concerns about increased use and the harms associated with strong opioids in the community.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The steep increase in opioid use has mainly been attributed to use for chronic noncancer pain.
- The increase in opioid use is associated with parallel increases in opioid-related morbidity and mortality, including dependence and overdose.
- It is unclear whether the prevalence and incidence of opioid use has changed in Australia in recent years.

WHAT THIS STUDY ADDS

- The prevalence of opioid use increased 0.6% between 2013 and 2017, with approximately 3 million adults using opioids each year.
- The incidence of opioid use decreased by 2.3% between 2013 and 2017, with approximately 1.9 million adults initiating opioids each year.
- The initiation of strong opioids has increased, reinforcing concerns about increased use and the harms associated with strong opioids in the community.

Introduction

Opioid use has increased rapidly in Australia and internationally over the past two decades [1, 2]. This increase is mainly attributable to greater opioid prescribing for chronic noncancer pain (CNCP) [3, 4]. Although the effectiveness of opioids has been established for acute [5] and cancer [6] pain, the long-term effectiveness in CNCP is uncertain [7]. Increasing opioid use has been associated with parallel increases in opioid-related morbidity and mortality, including dependence, hospitalizations and overdose [1, 8].

Opioid-related deaths appear most common in people aged <50 years [8–10]. Previous work examining strong opioid initiation among concessional beneficiaries in Australia identified that oxycodone was the most commonly initiated strong opioid, and that those initiating oxycodone were younger and less likely to have cancer [11]. The Australian Pain and Opioids In Treatment (POINT) study has found that people with CNCP taking opioids have complex demographic and clinical profiles, and a long history of pain [12]. Similar complex profiles have been described internationally among people with CNCP [13–16]. To date, no population-based studies have examined the initiation of all opioid analgesics in the Australian general adult population.

Following recent declines in annual prescribing rates in the US [17], it is unclear whether the prevalence and incidence of opioid use has changed in Australia in recent years. Additionally, comparisons of Australians who initiate opioids with and without a history of cancer have not been extensively described. Therefore, the objectives of the present study were to: (i) determine the prevalence and incidence of prescription opioid analgesic use in Australia between July 2013 and June 2017; and (ii) compare the characteristics of people with and without cancer initiating prescription opioid analgesics.

Methods

Study design and setting

We identified a nationally representative cohort of prevalent and incident opioid users between July 2013 and June 2017. Data were sourced from a random 10% sample of people who accessed subsidized medicines through Australia's Pharmaceutical Benefits Scheme (PBS). The Department of Human Services (DHS) subsidizes PBS prescriptions for Australian citizens, permanent residents and foreign visitors from countries with reciprocal healthcare agreements [18]. Two co-payment thresholds are set each year: a general co-payment (A$39.50 in 2018) and a concessional co-payment amount (A$6.40 in 2018). General beneficiaries are entitled to subsidized rates on higher-cost medicines priced above a set co-payment, whereas concessional beneficiaries (e.g. pensioners and those earning a low income) pay a reduced co-payment. Since July 2012, data have been available for all under co-payment dispensings from approved community pharmacies and private hospitals, and for outpatient and discharge dispensings from public hospitals in most states and territories (except NSW and the ACT). As most opioids are under co-payment for general beneficiaries, our study period commenced in July 2013, to obtain complete capture of opioid dispensings.

Opioid prevalence and incidence

All PBS-listed opioids available during the study period were included and defined according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system (Appendix Table A1). To obtain a 10% population sample, population data for adults aged 18–99 years from the Australian Bureau of Statistics were divided by 10 for each financial year (01 July–30 June). This was used as the denominator to determine the prevalence and incidence of opioid use [19]. To maintain confidentiality, we did not analyse data for people aged ≥100 years due to small numbers of people in this category. People with ≥1 opioid dispensing in each financial year were defined as prevalent opioid users. Therefore, prevalent users included both new (incident) users and continuous users from the previous financial years. To determine the prevalence of opioid use, the total number of opioid users was divided by the population-based denominator for each financial year. People initiating opioids were defined as those with no opioid dispensings in the 12 months prior to the opioid index date of supply. Therefore, the number of people aged 18–99 years initiating opioids was divided by the population-based denominator for each financial year to determine the incidence of use. As we used a 12-month look-back period to

define initiation, it is possible that a person initiated opioids more than once throughout the 4-year study period.

Characteristics of people initiating opioids

To explore further the characteristics of people initiating opioids, and to compare these among people with and without cancer, we also examined a range of variables, including opioid characteristics, prescriber specialty, medical comorbidities and other medicine use.

Opioid characteristics. Each person's initial opioid/s were further categorized as short acting, long acting or both; and weak opioid, strong opioid or both (Appendix Table A1). Individuals dispensed both a weak and strong opioid on the index date were categorized as having both strong and weak opioids. Similarly, individuals dispensed both a short-acting and long-acting opioid on the index date were categorized as having both short-acting and long-acting opioids. The administration route was categorized as oral, transdermal, other (intravenous, subcutaneous or intramuscular injections, buccal, rectal) and ≥2 routes (≥2 opioids dispensed on the index date with different routes). The initial opioid dispensings were categorized as concessional or general. The total oral morphine equivalents (OMEs), in mg, dispensed on the index date was calculated using the following formula: *Total OME mg dispensed = (pack strength*OME conversion factor of opioid dispensed*quantity dispensed)*. The OME conversion factors were adapted from published values by Nielsen *et al*. [20]. The total OME mg dispensed on the index date was calculated and categorized into five groups: total OME mg <100 [e.g. 10 tablets of oral oxycodone 5 mg (75 mg OME)]; 100–249 [e.g. 16 tablets of oral oxycodone 10 mg (240 mg OME)]; 250–499 [e.g. 30 tablets of oral oxycodone 10 mg (450 mg OME)]; 500–749 [e.g. 16 tablets of oral oxycodone 30 mg (720 mg OME)]; and ≥750 [e.g. 20 tablets of oxycodone 30 mg (900 mg OME)].

Prescriber specialty. The speciality of the prescriber for each opioid initiation was categorized consistently with the terminology used by the DHS [21]. For each prescription, the DHS provides a prescriber speciality code from a list of 196 codes which are included in the 10% random PBS sample. We categorized these codes into prescriber speciality of interest: general practitioner (GP) (codes 130, 132–134, 178, 184, 201, 202, 450); anaesthetist (specialist and nonspecialist) (codes 51, 60, 216); surgical specialist (codes 32–37, 39, 62, 73, 231, 232, 411); oncology specialist (codes 17, 49, 97, 804); intern (codes 160); dental practitioner (codes 102, 112, 115, 139, 143, 155, 156, 159); nurse practitioner (codes 651); other or missing.

Medical comorbidities. Medicines dispensed 12 months prior to and on the date of initial opioid dispensing were used to identify medical conditions using the validated RxRisk-V tool [22, 23]. We mapped the RxRisk-V tool to the International Classification of Diseases, Tenth Revision (ICD-10). To group these disease categories, we matched them to ICD-10 chapter groupings, as has been done in a previous study utilizing PBS data [11]. The RxRisk-V tool identifies fewer people with cancer than the Charlson's Comorbidity Index (43.2% *vs*. 67.2%) [22]. Therefore, a more comprehensive indicator for cancer was used that included other antineoplastic therapies, such as hormonal cancer therapies, which were not included in the original and updated RxRisk-V tool (Appendix Table A2).

Previous medicine use. Use of paracetamol, pregabalin and the PBS-subsidized nonsteroidal anti-inflammatory drugs (NSAIDs) were examined in the 3 months prior to and including the day of opioid initiation, in order to determine the recent non-opioid analgesic treatment of pain. This definition is consistent with previous published studies [11]. NSAIDs were further categorized into nonselective and cyclooxygenase 2 selective (Appendix Table A1). Recent use of PBS-subsidized benzodiazepines (Appendix Table A1) was also investigated as benzodiazepines are commonly implicated in opioid overdose deaths [24].

Statistical analyses

Characteristics are summarized as frequencies and percentages, means and standard deviations (SDs), or medians and

Table 1

Incidence and prevalence of opioid use in each financial year for people with and without cancer

	2013/2014	2014/2015	2015/2016	2016/2017
***N* (%)[a]**				
Incidence (people with cancer)	3077 (0.17)	3047 (0.16)	3133 (0.17)	3447 (0.18)
Incidence (people without cancer)	191 401 (10.52)	190 477 (10.31)	187 561 (9.99)	187 191 (9.80)
Incidence (all)	194 478 (10.67)	193 524 (10.47)	190 694 (10.16)	190 638 (9.98)
Prevalence (people with cancer)	14 822 (0.81)	15 026 (0.81)	14 943 (0.80)	14 320 (0.75)
Prevalence (people without cancer)	272 855 (14.99)	286 674 (15.51)	292 509 (15.59)	293 452 (15.37)
Prevalence (all)	287 677 (15.81)	301 700 (16.34)	307 452 (16.38)	307 772 (16.12)

[a]Percentage was determined using 10% of the Australian Bureau of Statistics population figures for people aged 18–99 years for the denominator for each financial year

interquartile ranges (IQRs). Pearson's chi-square test was used to compare proportions for categorical variables, and Student's *t*-test was used for continuous variables. The percentage distribution of types of opioids prescribed at initiation by prescriber speciality and according to age groups were presented graphically. Poisson regression was used to calculate rate ratios (RRs) for the prevalence and incidence of opioid use, comparing the period from 2013/2014 to 2016/2017. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 2

Baseline characteristics in the 365 days prior to, and on the day of, opioid initiation

	All (*n* = 769 334)	People without cancer (*n* = 756 630)	People with cancer (*n* = 12 704)	*P*-value[a,b]
N (%) or mean ± standard deviation				
Demographic characteristics				
Age, years	49.5 ± 18.9	49.2 ± 18.8	66.6 ± 14.8	<0.001
18–29	135 850 (17.7)	135 580 (17.9)	270 (2.1)	<0.001[c]
30–44	198 473 (25.8)	197 623 (26.1)	850 (6.7)	
45–54	128 692 (16.7)	127 424 (16.8)	1268 (10.0)	
55–64	119 340 (15.5)	116 823 (15.4)	2517 (19.8)	
65–74	99 260 (12.9)	95 586 (12.6)	3674 (28.9)	
75+	87 719 (11.4)	83 594 (11.1)	4125 (32.5)	
Sex, female	408 281 (53.1)	401 597 (53.1)	6684 (52.6)	0.299
Concessional beneficiary	300 249 (39.0)	292 000 (38.6)	8249 (64.9)	<0.001
Comorbidities[d]				
Total number[e]	2.7 ± 2.3	2.7 ± 2.3	4.7 ± 2.5	<0.001
Certain infectious and parasitic diseases	1987 (0.3)	1893 (0.3)	94 (0.7)	<0.001
Endocrine, nutritional and metabolic disorders	97 005 (12.6)	94 284 (12.5)	2721 (21.4)	<0.001
Mental and behavioural disorders	203 610 (26.5)	199 553 (26.4)	4057 (31.9)	<0.001
Alcohol dependence	1495 (0.2)	1481 (0.2)	14 (0.1)	0.030
Anxiety	62 570 (8.1)	61 366 (8.1)	1204 (9.5)	<0.001
Bipolar disorder	2297 (0.3)	2266 (0.3)	31 (0.2)	0.256
Dementia	3168 (0.4)	3079 (0.4)	89 (0.7)	<0.001
Depression	150 706 (19.6)	147 685 (19.5)	3021 (23.8)	<0.001
Nicotine dependence	17 346 (2.3)	17 135 (2.3)	211 (1.7)	<0.001
Psychotic illness	21 875 (2.8)	21 356 (2.8)	519 (4.1)	<0.001
Diseases of the nervous system	36 102 (4.7)	35 267 (4.7)	835 (6.6)	<0.001
Diseases of the circulatory system	280 017 (36.4)	271 370 (35.9)	8647 (68.1)	<0.001
Diseases of the respiratory system	109 686 (14.3)	107 234 (14.2)	2452 (19.3)	<0.001
Diseases of the digestive system	187 767 (24.4)	181 120 (23.9)	6647 (52.3)	<0.001
Diseases of the musculoskeletal system and connective tissue	49 738 (6.5)	46 926 (6.2)	2812 (22.1)	<0.001
Diseases of the genitourinary system	8481 (1.1)	8052 (1.1)	429 (3.4)	<0.001
Other	282 405 (36.7)	275 023 (36.4)	7382 (58.1)	<0.001

[a]Chi-square test
[b]Student's *t*-test
[c]A chi-square comparison between all the age groups
[d]Determined by the RxRisk-V tool
[e]Total number excluding pain and cancer

Ethical review

The Monash University Human Research Ethics Committee approved the study. The analysis plan and manuscript were approved by the Australian Government Department of Human Services.

Results

Opioid prevalence and incidence

There were 287 677 prevalent opioid users between July 2013 and June 2014, and 307 772 between July 2016 and June 2017

Table 3

Characteristics of opioids dispensed on the date of initiation

	All (*n* = 769 334)	People without cancer (*n* = 756 630)	People with cancer (*n* = 12 704)	*P*-value[a,b]
N (%) or median (interquartile range)				
Type of opioid				
Weak opioid	530 660 (69.0)	525 281 (69.4)	5379 (42.3)	<0.001
Strong opioid	220 445 (28.7)	213 363 (28.2)	7082 (55.8)	
Both weak and strong opioid	18 229 (2.4)	17 986 (2.4)	243 (1.9)	
Short acting	676 790 (88.0)	667 102 (88.2)	9688 (76.3)	<0.001
Long acting	65 883 (8.6)	63 784 (8.4)	2099 (16.5)	
Both short and long acting	26 661 (3.5)	25 744 (3.4)	917 (7.2)	
Route of administration				
Oral	750 478 (97.6)	738 751 (97.6)	11 727 (92.3)	<0.001
Transdermal	13 035 (1.7)	12 473 (1.7)	562 (4.4)	
Other	3652 (0.5)	3422 (0.5)	230 (1.8)	
≥2 routes	2169 (0.3)	1984 (0.3)	185 (1.5)	
Opioid dispensed				
Buprenorphine	10 990 (1.4)	10 622 (1.4)	368 (2.9)	<0.001
Codeine	33 852 (4.4)	33 207 (4.4)	645 (5.1)	<0.001
Fentanyl	2178 (0.3)	1972 (0.3)	206 (1.6)	<0.001
Hydromorphone	954 (0.1)	834 (0.1)	120 (0.9)	<0.001
Methadone	143 (0.0)	128 (0.0)	15 (0.1)	<0.001
Morphine	6671 (0.9)	5930 (0.8)	741 (5.8)	<0.001
Paracetamol/codeine	420 766 (54.7)	417 108 (55.1)	3658 (28.8)	<0.001
Oxycodone	182 021 (23.7)	177 293 (23.4)	4728 (37.2)	<0.001
Oxycodone/naloxone	24 270 (3.2)	23 282 (3.1)	988 (7.8)	<0.001
Tapentadol[c]	4209 (0.6)	4122 (0.5)	87 (0.7)	0.034
Tramadol	83 280 (10.8)	82 132 (10.9)	1148 (9.0)	<0.001
Oral morphine equivalents (OME), in mg dispensed				
Total OME[d]	60 (60–150)	60 (60–150)	150 (60–210)	<0.001
Total OME <100	462 692 (60.1)	458 275 (60.6)	4417 (34.8)	<0.001
Total OME 100–249	233 612 (30.4)	228 097 (30.2)	5515 (43.4)	
Total OME 250–499	49 005 (6.4)	47 358 (6.3)	1647 (13.0)	
Total OME 500–749	13 304 (1.7)	12 881 (1.7)	423 (3.3)	
Total OME ≥750	10 721 (1.4)	10 019 (1.3)	702 (5.5)	

[a]Chi-square test
[b]Student's *t*-test
[c]Tapentadol was Pharmaceutical Benefits Scheme listed in November 2013
[d]Example of initial OME of ~60 mg: eight tablets of oxycodone 5 mg (60 OME mg) or 20 tablets of paracetamol/codeine 500/30 mg (60 OME mg); initial OME of ~240 mg: 16 tablets of oxycodone 10 mg (240 OME mg) or 80 tablets of paracetamol/codeine 500/30 mg (240 OME mg)

(Table 1). From 2013/2014 to 2016/2017, there was an overall 0.6% increase {RR = 1.006 [95% confidence interval (CI) 1.004, 1.008]} in the prevalence of opioid use. Over the study period, the prevalence of opioid use decreased among people with cancer [RR = 0.974 (95% CI 0.967, 0.981)] and increased among people without cancer [RR = 1.008 (95% CI 1.006, 1.009)]. A total of 194 478 people initiated opioids between July 2013 and June 2014, and 190 638 people between July 2016 and June 2017, equating to 10.7% and 10.0% of the total adult Australian population, respectively (Table 1). There was an overall 2.3% decrease [RR = 0.977 (95% CI 0.975, 0.979)] in opioid initiation from 2013/2014 to 2016/2017. Among people initiating opioids who did not have a history of cancer, there was a 2.4% decrease [RR = 0.976 (95% CI 0.974, 0.978)] in opioid initiation and a 2.2% [RR = 1.022 (95% CI 1.006, 1.038)] increase in opioid initiation among people with cancer over the same period.

Characteristics of people initiating opioids

Demographics. In total, 769 334 people initiated opioids between July 2013 and June 2017. The mean (SD) age of the cohort was 49.5 (18.9) years and 53.1% were female (Table 2). There were 756 630 people initiating opioids without cancer, with a mean (SD) age of 49.2 (18.8) years. There were 12 704 people with cancer who initiated opioids, with a mean (SD) age of 66.6 (14.8) years.

Comorbidities. The mean (SD) number of comorbidities for all people initiating opioids was 2.7 (2.3) (Table 2). Among people without cancer, the mean (SD) number of comorbidities was 2.7 (2.3), compared with 4.7 (2.5) among those with cancer ($P < 0001$). Among all people initiating opioids, diseases of the circulatory system (36.4%), mental and behavioural disorders (26.5%) and diseases of the digestive system (24.4%) were common. Mental and behavioural disorders were more common among people with *vs.* without cancer (31.9% *vs.* 26.4%; $P < 0.001$), as were disorders of the circulatory system (68.1% *vs.* 35.9%; $P < 0001$) and digestive system (52.3% *vs.* 23.9%; $P < 0.001$).

Characteristics of initial opioid(s). Paracetamol/codeine was the most commonly dispensed opioid on initiation (54.7%), followed by single-ingredient oxycodone (23.7%) and tramadol (10.8%) (Table 3). The distribution of prescribed opioids by opioid type in each financial year and by age group are depicted in Figures 1 and 2. A strong opioid was initiated in 28.7% of the cohort and 8.6% were initiated on a long-acting opioid. The proportion of people initiating strong opioids increased from 26.0% to 31.6%, and the proportion of people initiating long-acting opioids increased from 8.0% to 9.5% between 2013/2014 and 2016/2017. The majority of people (97.6%) were initiated on oral opioid formulations. Most people (60.1%) initiating opioids had less than 100 mg in total OMEs dispensed [e.g. 10 tablets of oxycodone 5 mg (75 OME mg) or 20 tablets of paracetamol/codeine 500/30 mg (60 OME mg)]. Over half of the people with cancer (55.8%) initiated a strong opioid compared with 28.2% of people without cancer ($P < 0.001$). People with cancer had a median (IQR) of 150 (60–210) mg OMEs dispensed on initiation, compared with a median

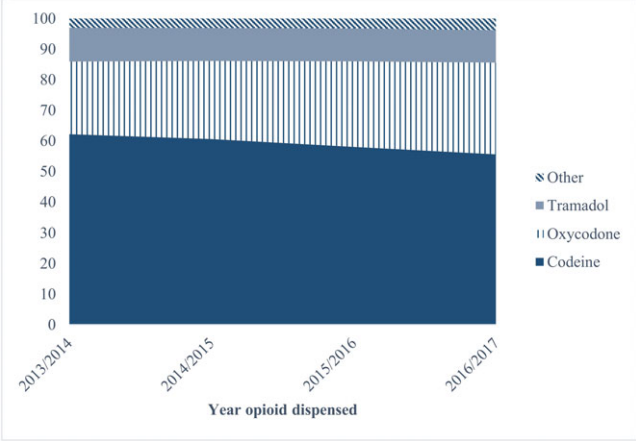

Figure 1
Proportion of opioids dispensed on initiation for each financial year

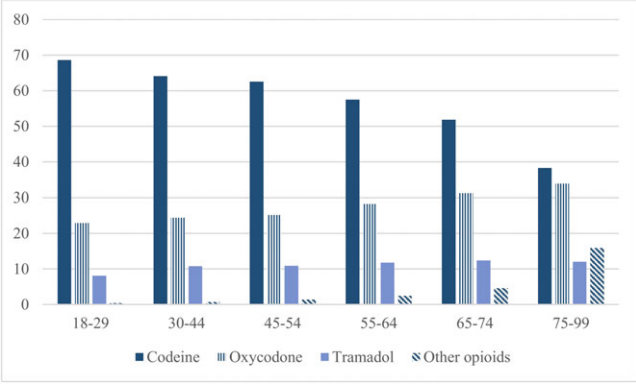

Figure 2
Percentage of each opioid type dispensed on initiation by age group between July 2013 and June 2017

(IQR) of 60 (60–150) mg OMEs among people without cancer. The proportion of people dispensed total OME <250 mg did not change over the 4-year study period (Appendix Table A3). People with cancer were more commonly dispensed a long-acting opioid (16.5% *vs.* 8.4%), oxycodone (37.2% *vs.* 23.4%) and oxycodone/naloxone (7.8% *vs.* 3.1%) than those without cancer ($P < 0.001$).

Prior medicine use. Non-opioid analgesics were used by 36.6% of people prior to opioid initiation, with NSAIDs being the most commonly (27.5%) used non-opioid analgesic (Table 4). Prior paracetamol (23.1% *vs.* 12.2%; $P < 0.001$) and pregabalin (6.8% *vs.* 3.5%; $P < 0.001$) use was more common among people with cancer compared with those without cancer, whereas NSAID use (27.6% *vs.* 21.5%; $P < 0.001$) was more common among people without cancer. Benzodiazepines were used by 13.2% of the cohort. Prior benzodiazepine use was more common among people with cancer than without cancer (22.6% *vs.* 13.0%; $P < 0.001$).

Table 4

Selected medicine use in the 3 months prior to, and on the day of, opioid initiation

	All (*n* = 769 334)	People without cancer (*n* = 756 630)	People with cancer (*n* = 12 704)	*P*-value[a]
Benzodiazepines	101 338 (13.2)	98 473 (13.0)	2865 (22.6)	<0.001
Alprazolam	3165 (0.4)	3098 (0.4)	67 (0.5)	0.039
Diazepam	49 569 (6.4)	48 765 (6.5)	804 (6.3)	0.596
Nitrazepam	3267 (0.4)	3143 (0.4)	124 (1.0)	<0.001
Oxazepam	12 891 (1.7)	12 503 (1.7)	388 (3.1)	<0.001
Temazepam	45 557 (5.9)	43 687 (5.8)	1870 (14.7)	<0.001
Non-opioid analgesics	281 365 (36.6)	276 069 (36.5)	5296 (41.7)	<0.001
Paracetamol[b]	95 315 (12.4)	92 382 (12.2)	2933 (23.1)	<0.001
Pregabalin	27 401 (3.6)	26 539 (3.5)	862 (6.8)	<0.001
NSAIDs	211 428 (27.5)	208 691 (27.6)	2737 (21.5)	<0.001
Selective COX-2 inhibitors	106 821 (13.9)	105 184 (13.9)	1637 (12.9)	0.001
Meloxicam	62 434 (8.1)	61 529 (8.1)	905 (7.1)	<0.001
Celecoxib	48 563 (6.3)	47 770 (6.3)	793 (6.2)	0.743
Nonselective NSAIDs	118 971 (15.5)	117 704 (15.6)	1267 (10.0)	<0.001
Diclofenac	42 001 (5.5)	41 579 (5.5)	422 (3.3)	<0.001
Ibuprofen	35 306 (4.6)	35 002 (4.6)	304 (2.4)	<0.001
Naproxen	26 518 (3.5)	26 183 (3.5)	335 (2.6)	<0.001
Indomethacin	13 901 (1.8)	13 730 (1.8)	171 (1.4)	<0.001
Piroxicam	3466 (0.5)	3423 (0.5)	43 (0.3)	0.057
Mefenamic acid	2682 (0.4)	2675 (0.4)	7 (0.1)	<0.001
Ketoprofen	1627 (0.2)	1596 (0.2)	31 (0.2)	0.421

COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug
[a]Chi-square test
[b]Since January 2016, paracetamol has no longer been subsidized on the Pharmaceutical Benefits Scheme

Prescriber specialty. Approximately half of all opioid initiations were by GPs (51%) (Appendix Figure A1). Codeine was the most commonly prescribed opioid by dental practitioners (97.7%), GPs (67.9%) and nurse practitioners (61.7%). Oxycodone was the most commonly prescribed opioid by interns (65.6%), oncology specialists (57.2%), surgical specialists (47.0%) and anaesthetic specialists and nonspecialists (43.8%) (Figure 3).

Discussion

This is the first study to report the prevalence and incidence of opioid use in Australian adults. Approximately 16% of the adult population use opioids each financial year, and the prevalence of opioid use increased by 0.6% over the study period. The rate of opioid initiation decreased by 2.3% over the study period, with approximately 10% of adults initiating opioids each financial year. Paracetamol/codeine, followed by single-ingredient oxycodone and tramadol, were the most commonly prescribed opioids on initiation, with codeine use declining in the previous 2 years and oxycodone use increasing. Approximately half of all opioid initiations were by GPs.

Extrapolating to the total population, each year over 1.9 million adults (10%) are estimated to initiate opioids and over 3 million adults (16%) are using opioids in Australia. The prevalence of opioid use in Australia is similar to the 14% prevalence in Ontario, Canada [25]. Despite increasing prescribing rates between 2006 and 2010 in the US, annual prescribing rates declined from 81.2 to 70.6 per 100 persons between 2010 and 2015 [17]. Our results also demonstrate a decrease (2.3%) in overall opioid initiation in Australian adults since 2013/2014. In light of increasing concerns about opioid-related harms, it is encouraging that the rate of opioid initiation appears to be decreasing. However, it is not known whether the decrease in opioid initiation has translated to a decrease in harm. The total OME amount dispensed on initiation has remained relatively stable over the 4-year study period. However, the proportion of people initiating strong or long-acting opioids has increased over the same period. This is concerning because strong and long-acting opioids have been linked to harms in both the US [26] and Australia [9].

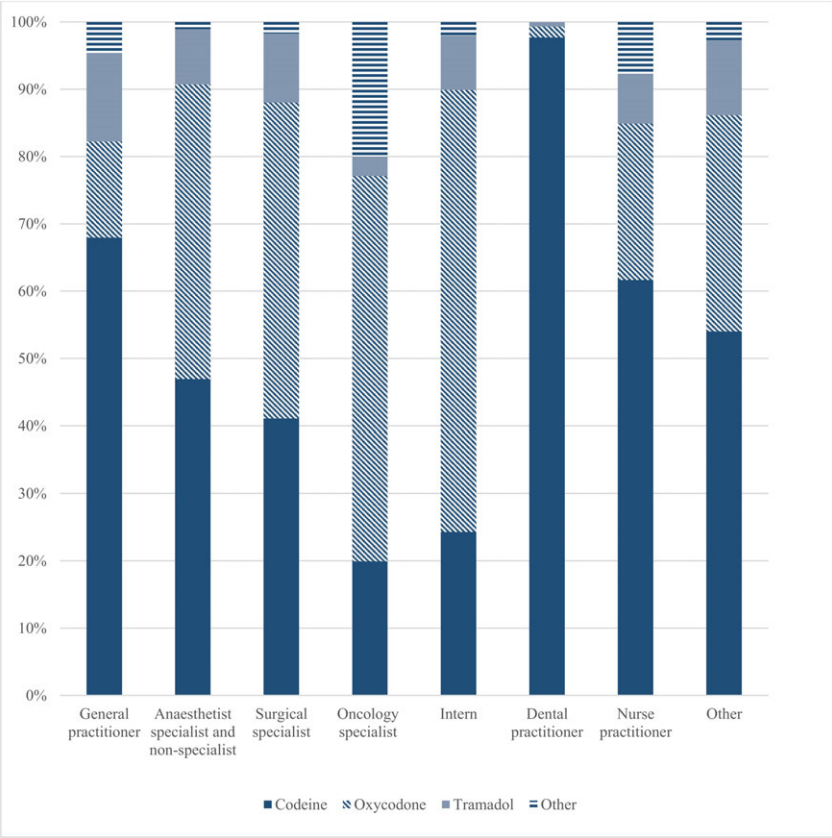

Figure 3

Percentage of opioids initiated by prescriber specialities of interest between July 2013 and June 2017. *Other category for oncology specialists:10.7% morphine, 4.8% fentanyl and 4.5% buprenorphine, tapentadol and methadone

Therefore, future studies should investigate the impact of recent changes in opioid use on opioid-related harm in Australia. Our study supports recent calls from the Therapeutic Goods Administration for a review of current practice and policy related to opioid prescribing [27].

Previous research investigating opioid use in Australia and the US attributed the overall increase in opioid use to their increase in use for CNCP [3, 4, 28]. In our study, previous non-opioid analgesic use was higher among people with cancer compared with those without cancer. CNCP management is complex and requires individualization [29]. Although multimodal strategies for CNCP are recommended [29], in our study only one-third of people without cancer had used non-opioid analgesics in the previous 3 months. Therefore, our results may suggest suboptimal treatment with non-opioid analgesics, particularly in those with CNCP, where opioid use should be reserved for those who are unresponsive to optimized non-opioid therapies [29, 30]. However, data were not available on non-opioid analgesics purchased over the counter and therefore may underestimate non-opioid analgesic use. Additionally, no data were available on prescriptions that were issued by prescribers but never dispensed in pharmacies (e.g. people who successfully trialled non-opioids first and decided not to fill their opioid prescription). Nevertheless, non-opioid treatment modalities should be trialled first, to reduce inappropriate long-term opioid use and minimize harm. A US study found that 5% of opioid initiators became long-term users, defined as ≥6 opioid prescriptions in the 12 months following the initiation month [16]. They also found that long-term use was, in turn, associated with a higher risk of opioid-related hospitalization [16]. A recent study in Australia, using group-based trajectory modelling to define persistent use, found that 2.6% of adults initiating opioids became persistent users over a 12-month period [31].

In order to identify risk mitigation strategies for opioid-related harm, we examined prescriber specialty and the characteristics of the initial opioid. We found that approximately half of all opioid initiations were by GPs. Similarly, US studies have reported that primary care specialities prescribed 44.5% of dispensed opioid prescriptions in 2012 [32]. As pain conditions account for at least 11% of all conditions managed by GPs in Australia [33], it is not surprising that half of all opioid initiations were by GPs. Yet, previous research in the US reported that of all specialities prescribing opioids, primary care specialities were most often associated with opioid fatalities [34]. This is concerning as, although Australia has followed a similar trend to the US in opioid-related harm, to date there have been minimal regulatory, policy or programmatic shifts in response [35]. Although interns are responsible for 8.3% of all opioids initiated, we found that oxycodone was the most commonly prescribed opioid by this group (65.6%). Interns

usually prescribe medicines on discharge from hospitals in Australia under the guidance of the specialty team. The proportion of interns prescribing opioids provides important information regarding opioid initiation from hospitals. However, this may be underestimated as prescriptions dispensed at hospitals in NSW and the ACT are not captured in this dataset.

Strengths and limitations

The key strength of our study was the use of data from a 10% random sample of people accessing medicines through the PBS over a period when under co-payment data were captured. Although we captured more than 80% of prescription opioid use in Australia, data on private non-PBS prescriptions and over-the-counter analgesics were not captured [27]. The subsidy of paracetamol and tapentadol has changed throughout the study period. Since January 2016, paracetamol has no longer been subsidized on the PBS. This means that the estimate of prior paracetamol use since 2016 may be an underestimate of actual use. Tapentadol was approved for listing on the PBS in November 2013. Therefore, its lower utilization compared with other opioids may reflect a slower uptake by prescribers. Additionally, opioid initiation for hospital inpatients in all States and on discharge from hospitals in NSW and the ACT were not captured in this dataset. Therefore, our study does not necessarily reflect the characteristics of all adults initiating opioids in Australia. As PBS data are based on dispensing records, we do not know whether and how the medicine was taken. In the absence of comorbidity data, we used dispensing data to identify treatment for specific medical conditions. Although we used a comprehensive list of cancer medicines, some people with cancer may not have had cancer medicines dispensed and therefore may have been misclassified. Additionally, people may have been categorized into the noncancer group if they had a first dispensing of a cancer medicine after opioid initiation. Clinical information, including the indication for opioid initiation, dose, duration and severity of pain, was not available in our dataset.

Conclusion

Rates of opioid use in Australia have remained high since 2013, with approximately 3 million adults using opioids and over 1.9 million adults initiating opioids each year. There has been a slight increase in the prevalence of opioid use but a decrease in incidence in the 4-year period between 2013 and 2017. People without cancer account for the majority of opioid use and are more likely to be initiated on short-acting and weak opioids. The proportion of people initiating on strong opioids has increased over time, reinforcing concerns about the increase in the use and harms associated with strong opioids in the community.

Competing Interests

The authors have no known or potential conflicts of interest to declare. S.L. is supported through an Australian Government Research Training Program Scholarship. J.I. and N.G. are supported by the NHMRC Early Career Fellowship Scheme (grant numbers #1072137 and #1091878). J.S.B. is supported by a NHMRC Dementia Leadership Fellowship (grant number #1140298).

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Appendix

Table A1

Name of medicines used in analyses and their corresponding Anatomical Therapeutic Classification codes[a]

Medicine name	Anatomical Therapeutic Classification code
Paracetamol	N02BE01
Pregabalin	N03AX16
NSAIDs	M01AB01-M01AH06
Nonselective	
• **Diclofenac**	M01AB05
• **Ibuprofen**	M01AE01
• **Indomethacin**	M01AB01
• **Ketoprofen**	M01AE03
• **Mefenamic acid**	M01AG01
• **Naproxen**	M01AE02
• **Piroxicam**	M01AC01
COX-2 selective	
• **Celecoxib**	M01AH01
• **Meloxicam**	M01AC06
Benzodiazepines	N05BA, N05CD
• **Diazepam**	N05BA01
• **Oxazepam**	N05BA04
• **Bromazepam**	N05BA08
• **Alprazolam**	N05BA12
• **Nitrazepam**	N05CD02
• **Flunitrazepam**	N05CD03
• **Temazepam**	N05CD07
• **Midazolam**	N05CD08
Opioids	NO2A, R05DA04
Weaker opioids	
• **Codeine**	R05DA04
• **Combination codeine preparations**	N02AA59, N02AJ06
• **Tramadol**	N02AX02
• **Tapentadol**	N02AX06
Stronger opioids	
• **Morphine**	N02AA01
• **Hydromorphone**	N02AA03
• **Oxycodone**	N02AA05
• **Oxycodone/naloxone**	N02AA55
• **Fentanyl**	N02AB03
• **Methadone**	N02AC52
• **Buprenorphine**	N02AE01

COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug

[a]ATC/DDD Index 2018: World Health Organization; 2017 [19/05/18]. Available from: https://www.whocc.no/atc_ddd_index/

Table A2

RxRisk-V categories and corresponding Anatomical Therapeutic Classification codes

Disease category	Anatomical Therapeutic Classification codes
Alcohol dependence	N07BB01-N07BB99
Allergies	R01AC01-R01AD60, R06AD02-R06AX27, R06AB04
Anticoagulation	B01AA03-B01AB06, B01AE07, B01AF01, B01AF02, B01AX05
Antiplatelet	B01AC04-B01AC30
Anxiety and tension	N05BA01-N05BA56, N05BE01
Arrhythmias	C01AA05, C01BA01-C01BD01, C07AA07
BPH	G04CA02-G04CA03, G04CB01, G04CB02, C02CA01
Bipolar disorder	N05AN01
CHF/hypertension	[C03CA01-C03CC01 AND (C09AA01-C09AA16 OR, C09CA01 - C09CX99)], C03DA04, C07AB07, C07AG02, C07AB12, C09DX04, C07AB02_2
Dementia	N06DA02-N06DA04, N06DX01
Depression	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX26
Diabetes	A10AA01-A10BX08
End-stage renal disease	B03XA01-B03XA03, V03AE02, V03AE03, V03AE05
Epilepsy	N03AA01-N03AX30
Gastric acid disorder	A02BA01-A02BX77
Glaucoma	S01EA01-S01EB03, S01EC03-S01EX02
Gout	M04AA01-M04AC01
Hepatitis B	J05AF08, J05AF10, J05AF11
Hepatitis C	J05AE11-J05AE15, J05AX14-J05AX68, J05AB04, L03AB11, L03AB60, L03AB61
HIV	J05AE01-J05AE10, J05AF01-J05AF07, J05AF09, J05AF12-J05AG05, J05AR01-J05AR19, J05AX07-J05AX09, J05AX12
Hyperkalaemia	V03AE01
Hyperlipidaemia	C10AA01-C10BX12
HTN	C03AA01-C03BA11, C03BB04, C03DA01-C03DA03, C03EA01-C03EA14, C09BA02-C09BA15, C09DA01-C09DA09, C02AB01-C02AC05, C02DB01-C02DB04, C03DB01-C03DB02
Hypothyroidism	H03AA01-H03AA05
IHD/angina	C01DA02-C01DA70, C01DX16, C08EX02
IHD/HTN	C07AA01-C07AA06,C07AG01, C08CA01-C08DB01, C09DB01-C09DB08, C09DX01-C09DX03, C09BB02-C09BB12, C07AB03, C07AB02_1
IBD	A07EC01-A07EC04,A07EA01-A07EA02, A07EA06, L04AA33
Liver failure	A07AA11
Malignancy	L01AA01-L01AX04, L01BA01_2, L01BA03- L01XX53, L02BG03, L02BG04, L02BG06, L02BB01-L02BB04, L02BX01-L02BX03, L04AX02, L04AX04, L04AX06, L02BA01_01, L02AE03_1, L02AE02_1
Malnutrition	B05BA01-B05BA10
Migraine	N02CA01-N02CX01
Osteoporosis/Paget's disease	M05BA01-M05BB08, M05BX03, M05BX04, H05AA02
Pain[a]	N02AA01-N02AX99, R05DA04
Pain/inflammation	M01AB01-M01AH06
Pancreatic insufficiency	A09AA02
Parkinson's disease	N04AA01-N04BX03

(continues)

Table A2

(Continued)

Disease category	Anatomical Therapeutic Classification codes
Psoriasis	D05AA, D05BB01-D05BB02, D05AX02, D05AC01-D05AC51, D05AX52
Psychotic illness	N05AA01-N05AB02, N05AB06-N05AL07, N05AX01-N05AX17
Reactive airway disease	R03AC02-R03DC03, R03DX05
Nicotine dependence	N07BA01-N07BA03, N06AX12
Steroid-responsive conditions	H02AB01-H02AB17
Transplant	L04AA06, L04AA10, L04AA18, L04AD01, L04AD02, L04AC02
Tuberculosis	J04AB02, J04AC01-J04AM06

BPH, benign prostatic hypertrophy; CHF, congestive heart failure; HTN, hypertension; IBD, inflammatory bowel disease; IHD, ischaemic heart disease; HIV, human immunodeficiency virus

[a]Where the ATC code has _01 or_02 at the end, this can be used for multiple indications; therefore, to separate indications based on Pharmaceutical Benefits Scheme item codes, these additional digits were used.

Table A3

Total oral morphine equivalents (OMEs), in mg, dispensed on initiation in each financial year

	2013/2014	2014/2015	2015/2016	2016/2017
***N* (%)**				
Total OME mg dispensed				
<100	120 304 (61.9)	117 918 (60.9)	113 531 (59.5)	110 939 (58.2)
100–249	56 489 (29.1)	57 846 (29.9)	58 917 (30.9)	60 360 (31.7)
250–499	11 704 (6.0)	11 884 (6.1)	12 364 (6.5)	13 053 (6.9)
500–749	3236 (1.7)	3263 (1.7)	3323 (1.7)	3482 (1.8)
≥750	2745 (1.4)	2613 (1.4)	2559 (1.3)	2804 (1.5)

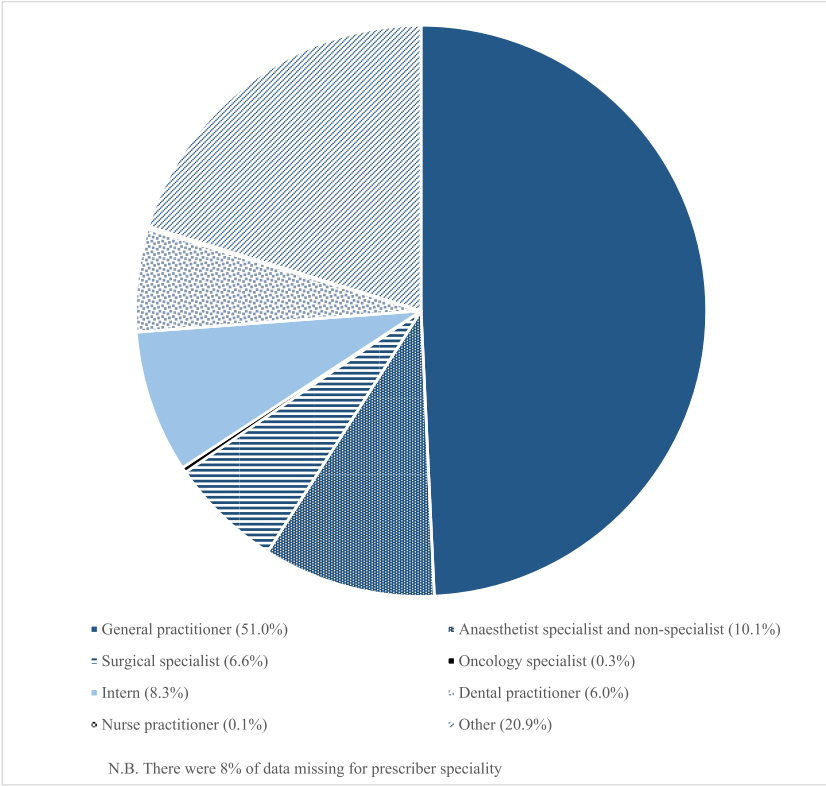

Figure A1
Proportion of opioids initiated during the study period by each prescriber speciality

Chapter Four - Predictors of persistent prescription opioid analgesic use among people without cancer in Australia

Chapter Three identified that 3 million adults use opioids and 1.9 million adults initiate opioids each year in Australia. The patterns of prescription opioid analgesic use after initiation were unclear. Understanding whether people continue to take prescription opioid analgesics after initiation is important because there is evidence of harm with persistent opioid use as discussed in Chapter One. Additionally, identifying the characteristics of those who use prescription opioid analgesics long-term is important in recognising those that may be at greater risk of harm. As discussed earlier in the thesis, long-term opioid use has been identified as a 'problematic' pattern of opioid use by the CDC.

This chapter explores persistent prescription opioid analgesic use in the Australian population using a novel method. Group based trajectory modelling was used to determine the pattern of prescription opioid analgesic use over a 12-month period. This method was key to defining opioid persistence because opioid use may change over time and is difficult to define using explicit criteria. Some of the risk factors for extramedical use identified in the scoping review in Chapter Two including benzodiazepine use, age and gender were also investigated as predictors in this study.

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ORIGINAL ARTICLE

Predictors of persistent prescription opioid analgesic use among people without cancer in Australia

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Keywords non-cancer pain, opioid analgesics, persistent use, pharmacoepidemiology, predictors

AIMS

To identify patterns of opioid analgesic use and determine predictors of persistent opioid use among people without cancer.

METHODS

A population-based cohort study of Australians initiating prescription opioids from July 2013 to December 2015 was conducted using data from a random 10% sample of people who accessed medicines through Australia's Pharmaceutical Benefits Scheme. A 12-month retrospective period was used to define opioid initiation, exclude people with cancer and determine comorbidities. Persistent use over 12 months since initiation was identified through group-based trajectory modelling. Odds ratios (OR) and 95% confidence intervals (CIs) for predictors of opioid persistence were estimated using logistic regression.

RESULTS

The cohort consisted of 431 963 people without cancer who initiated opioids. A total of 11 323 (2.6%) persistent opioid users were identified. Predictors of persistence included initiation with transdermal formulations (OR 4.2, 95% CI 3.9–4.5), or initiation with total oral morphine equivalents (OME) ≥ 750 mg (3.7, 3.3–4.1), having depression (1.6, 1.5–1.7) or psychotic illness (2.0, 1.9–2.2). Previous dispensing of paracetamol (2.0, 1.9–2.1), pregabalin (2.0, 1.8–2.1) and benzodiazepines (1.53, 1.4–1.6) predicted persistence. Compared to people aged 18–44 years, those ≥75 years were 2.5 (2.3–2.6) times more likely to be persistent users.

CONCLUSIONS

Patient-specific characteristics (older age, prior history of mental health comorbidities and use of non-opioid analgesics) and prescriber choice of initial opioid (transdermal formulation and higher total OMEs) were found to strongly predict persistent use. This information may help prescribers target monitoring and early intervention efforts in order to prevent harms associated with the long-term use of opioids.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Long-term opioid analgesic use for chronic non-cancer pain is associated with uncertain clinical benefits but clear harms.
- In the United States, characteristics of the initial opioid prescription, such as number of days supplied and cumulative dose ≥700 mg oral morphine equivalents (OMEs), predicted continued opioid use.

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WHAT THIS STUDY ADDS

- Of people without cancer who initiate opioids in Australia, 2.6% go on to become persistent users over a 12-month period.
- Patient-specific characteristics (older age, prior history of mental health comorbidities and use of non-opioid analgesics) and initial prescriber choice of opioid (transdermal formulation and higher OMEs) were found to strongly predict persistent opioid use.

Introduction

Chronic non-cancer pain (CNCP) is highly prevalent worldwide [1] and has been shown to have a marked negative effect on functional capacity and quality of life [2, 3]. Treatment of CNCP requires individualization of both non-pharmacological and pharmacological interventions; however, prescribing opioids for CNCP remains controversial and multiple best-practice guidelines have been published to minimize inappropriate use and harms [4, 5]. It is estimated that the worldwide use of opioid analgesics has doubled over the past decade to 7.35 billion defined daily doses per annum [6]. Opioid utilization in the United States (US), Canada, Western Europe, Australia and New Zealand is particularly high. These countries collectively account for 17% of the world's population but 92% of overall opioid utilization [7]. Although the increase in utilization alone is not necessarily problematic, long-term opioid analgesic use has been associated with excess morbidity and mortality worldwide, including harm resulting from misuse [8–11].

Despite uncertainty about the benefits of long-term opioid analgesic use in the treatment of CNCP, there is clear evidence of significant harms [12]. In order to reduce harm from long-term opioid analgesic use, it is firstly necessary to understand who is at greatest risk of long-term or persistent use. A recent US study found that characteristics of the initial opioid prescription such as number of days supplied and cumulative dose ≥700 mg oral morphine equivalents (OMEs) predicted continued opioid use for up to 3 years following treatment of acute pain [13]. Furthermore, Quinn *et al*. [14] found people with depressive disorders had double the risk of transitioning to long-term opioid use, as did people who were dispensed benzodiazepines prior to opioid initiation. Moreover, Thielke *et al*. [15] found that the likelihood of long-term opioid use was increased among those with higher problem opioid risk scores. This score, found to predict problem opioid use, is a composite measure of a range of individual characteristics including age ≤65 years, being a current smoker and having a history of a mental health disorder, hepatitis C, and abuse/dependence with opioids, alcohol or other substances [16]. Rogers *et al*. [17] found that poorer self-reported physical functional level was the strongest predictor of long-term opioid use in people with concessional beneficiaries and aged ≥45 years in New South Wales, Australia.

The predictors of long-term opioid analgesic use have not previously been studied in all of Australia. This knowledge is necessary to enable clinicians to consider and reduce the future risk of harms at the time of treatment initiation. Currently, clinical treatment guidelines recommend that specific tools and instruments (e.g. the Opioid Risk Tool and Screener and Opioid Assessment of Patients with Pain) be used to predict the risk of future aberrant drug-related behaviours [5]. However, these tools do not necessarily identify people who are at greatest risk of long-term use or harm not associated with aberrant drug-related behaviours. Therefore, we sought to identify trajectories of prescription opioid analgesic use and determine predictors of persistent opioid analgesic use among people without cancer in Australia.

Methods

Study design and setting

We undertook a retrospective population-based cohort study of people who initiated prescription opioid analgesics between July 2013 and December 2015 in Australia using data from a random 10% sample of people who accessed medicines through Australia's Pharmaceutical Benefits Scheme (PBS). The PBS is a national government-funded system that subsidizes prescription medicines for citizens, permanent residents and foreign visitors from countries with reciprocal health care agreements [18]. For research purposes, the Australian Government Department of Human Services provides access to a 10% random sample of people accessing medicines through the PBS [18]. This sample is considered representative of PBS dispensing for all Australian residents. At the end of 2016, Australia had an estimated total population of 24 million [19].

Since July 2012, all dispensings for PBS-listed medicines in approved community pharmacies, private hospitals and some public hospitals (excluding dispensings during admission as an inpatient in hospital) have been captured in PBS records. Concessional beneficiaries (e.g. pensioners and low-income earners) are entitled to subsidized rates on all PBS-listed medicines and pay a reduced co-payment amount, while general beneficiaries are entitled to subsidized rates on higher-cost medicines priced above a set co-payment amount. As of 1 January 2018, the maximum co-payment for concessional beneficiaries is AUD6.40 (USD5.02) and AUD39.50 (USD30.97) for general beneficiaries [20]. The study period was chosen to reflect the period during which data on dispensings of under co-payment medicines were first recorded in the PBS dataset. As of 2013, PBS dispensing records are estimated to account for more than 80% of prescription opioid use in Australia [21]. The dataset captures medicine information including name, strength, quantity, item code, date dispensed, date prescribed and number of repeats authorized. The dose prescribed, duration of treatment and indication for medicine use are not available.

Study population

Adults aged ≥18 years who were new opioid users between July 2013 and December 2015 were included to allow for a follow-up period of 12 months (Figure 1). As the dataset does not provide actual age for people ≥100 years, we excluded those who were ≥100 years. New users were defined as those with no preceding opioid dispensings in the 12 months prior to the initial opioid dispensing. As the focus of this study was on people without cancer (i.e. non-cancer pain), we excluded those with evidence of a dispensing for a cancer medicine (Appendix S1) at baseline or in the 12 months prior to initiating prescription opioid analgesics. We also excluded people who died (n = 9103, 1.6%) during the follow-up period.

Definition of persistent opioid use

We defined persistent/non-persistent opioid use using two steps. Firstly, people who were dispensed opioids only at baseline were all categorized as non-persistent users (Figure 1). For the remainder of the cohort (i.e. those dispensed opioids in at least two months), persistent use was identified through a group-based trajectory model (GBTM) [22, 23]. Although, there are several methods for studying medication persistence, we opted to use GBTM to define persistence as prior research has found that the number of people identified as continuing long-term use of opioids varies depending on the explicit criteria used to define persistence [24]. Additionally, when using explicit criteria, there is no single appropriate definition of long-term opioid use and the definition applied should depend on the specific research question [24]. Consequently, we opted to use a GBTM which avoids the need for explicit criteria defining persistence to be specified. Instead, persistence was defined by the patterns of opioid dispensings for the cohort over a 12-month period following initiation [25, 26]. For each month, we created a binary variable that indicates whether an opioid dispensing occurred during that month or not. Using patterns of dispensings, people were assigned to various trajectories based on the highest estimated probability that they belong in that group. A third-order trajectory model with four groups was determined to have the best overall model fit based on

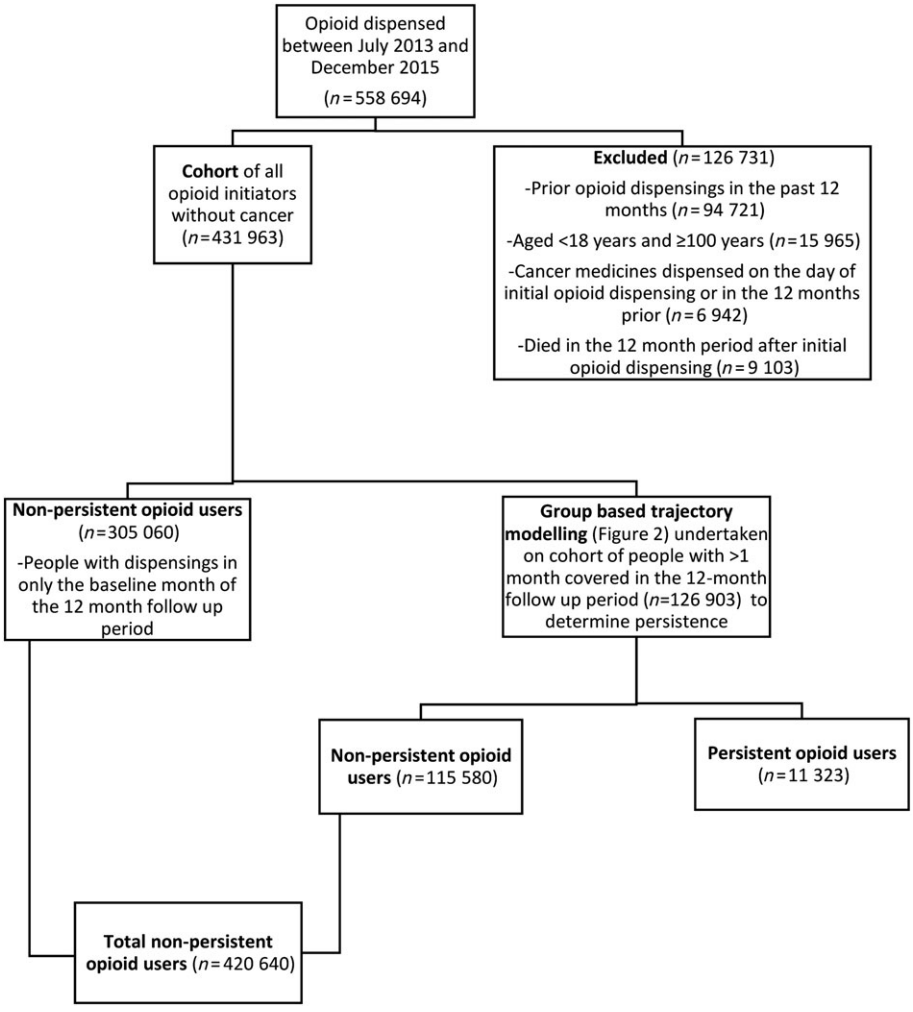

Figure 1
Flow diagram of study cohort

the highest Bayesian information criterion (BIC) value, convergence and an estimated probability of group membership of ≥5% [23]. Those assigned to Trajectory 4 (shown in Figure 2) were defined as persistent users, while those assigned to Trajectories 1–3 were collectively defined as non-persistent users. The total number of non-persistent users in the cohort included individuals who were only dispensed opioids at baseline as well as those assigned to Trajectories 1–3.

Baseline opioid use

The opioid at the initial dispensing was categorized as either strong or weak. Strong opioids included [27]: morphine (Anatomical Therapeutic Chemical [ATC] code N02AA01), oxycodone (N02AA05, N02AA55), buprenorphine (N02AE01), fentanyl (N02AB03), hydromorphone (N02AA03) and methadone (N02AC52). Weak opioids included [27]: single-ingredient codeine (R05DA04) and combination codeine preparations (N02AA59, N02AJ06), tramadol (N02AX02) and tapentadol (N02AX06). Individuals dispensed both a weak and strong opioid at baseline were categorized as having initiated a strong opioid. The route of administration was categorized as oral, transdermal or other (intravenous, subcutaneous or intramuscular injections, buccal, rectal). For the initial opioid dispensing, the total oral morphine equivalent (OME) amount dispensed was calculated using the following formula:

$$\text{Total OME dispensed} = (\text{pack strength}^{*} \times \text{OME conversion factor of opioid dispensed}^{*} \times \text{quantity dispensed})$$

The OME conversion factors (Appendix S2) were adapted from published values by Nielsen *et al*. [28]. The total baseline OME dispensed was categorized into four groups: total OME < 250, 250–499, 500–749 and ≥750. The subsidy level of the initial opioid dispensing was categorized as concessional (marker of lower socioeconomic status) or non-concessional.

Medical conditions and comorbidities

RxRisk-V was used to provide a measure of comorbidity for each person [29]. The RxRisk-V tool uses records of dispensed medicines to identify existing medical conditions from 45 ATC code groups. An adaptation of the RxRisk-V tool was used incorporating ATC codes for newly registered medicines to ensure potential comorbidities were not missed (Appendix S1). Australian findings have previously indicated that the RxRisk-V tool identified fewer people with cancer compared to the Charlson comorbidity index which is widely used to assess disease burden (43.2% *vs*. 67.2%) [30] and hence, we developed a more comprehensive indicator of cancer to capture other antineoplastic therapies such as hormonal cancer therapies. Comorbidities of particular interest were depression, psychotic illness, alcohol and nicotine dependence, as these have previously been shown to predict persistent use of opioids [13–15]. The total number of other comorbidities identified using RxRisk-V (excluding comorbidities of particular interest) were classified into four groups: 0, 1–2, 3–4 and ≥5.

Previous medicine use

To assess previous pain treatment, we also examined use of non-opioid analgesics at baseline and in the 12 months prior to initiating an opioid analgesic. These included: paracetamol (N02BE01), pregabalin (N03AX16) and non-steroidal anti-inflammatory drugs (NSAIDs) (M01AB01–M01AH06). Use of psychotropic medicines that are commonly implicated in opioid overdose [31, 32], were also examined at baseline and in the 12 months prior to opioid initiation and included benzodiazepines (N05BA, N05CD) and stimulants (N06BA, N06BC).

Statistical analyses

Baseline characteristics of the cohort are presented as frequencies and percentages or means and standard deviations (SD). Multivariable logistic regression was used to identify predictors for persistent opioid use compared to non-persistent use and to calculate adjusted odds ratios (ORs) and 95% confidence intervals (95% CI). Predictors included age, sex, concessional status, characteristics of the initial

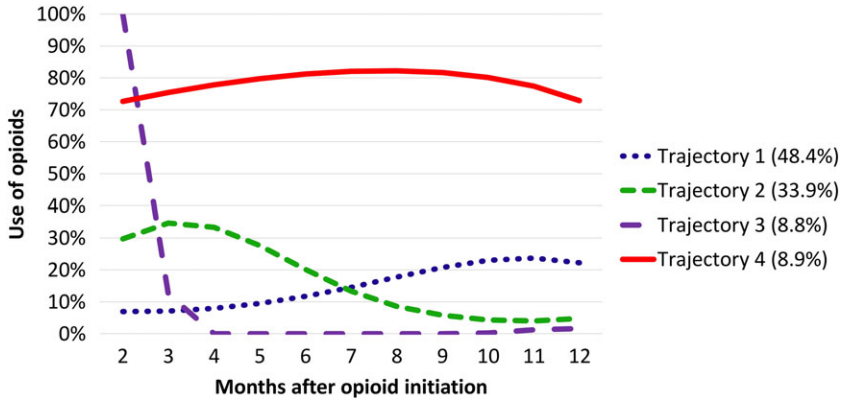

Figure 2

Trajectories of opioid use in people dispensed opioids in >1 month. Persons in Trajectory 4 (8.9% of those included in the group-based trajectory model) persistently used opioids in the 12 months following initiation. Persons in Trajectories 1 (48.4%), 2 (33.9%) and 3 (8.8%) were collectively considered as non-persistent users, as the patterns of the trajectories suggest minimal opioid dispensings over the 12-month follow-up

opioid dispensing (strong opioid, total OME dispensed and route of administration), depression, psychotic illness, alcohol dependence, nicotine dependence, migraine, total number of other comorbidities, and prior use of benzodiazepines, paracetamol, NSAIDs, pregabalin and stimulants. Multicollinearity between variables was assessed using variance inflation factors, tolerance and eigenvalues. There was no evidence of multicollinearity between predictors in the final model. The c statistic of the logistic regression model was used to evaluate the explanatory power of the model. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analyses

We repeated the main analysis by stratifying across three age groups (18–64, 65–84 and ≥85 years) to assess whether the strength of the predictors vary across age. To explore the effect of our definition of persistence, we conducted a sensitivity analysis by using an alternative definition of persistence which identifies non-persistence based on gaps between months with opioid dispensings. All opioid initiators without cancer who had ≥3 consecutive months without an opioid dispensing were defined as non-persistent users. Those who had a gap of ≤2 consecutive months without an opioid dispensing in the 12-month period were defined as persistent users.

Ethical review

The study was approved by the Monash University Human Research Ethics Committee.

Results

Cohort

The cohort consisted of 431 963 people without cancer who were initiated on opioids (Figure 1). Baseline characteristics are described in Table 1. The mean (SD) age for the final cohort was 48.4 (18.4) years and 53.0% were female. The mean (SD) total number of comorbidities (excluding those of particular interest) for the cohort was 2.3 (2.1). Paracetamol/codeine was the most common opioid initiated (57.8%), followed by oxycodone (26.1%). The 9103 people that were excluded from the study due to death were older (79 (13.7) years) and had higher mean total OME dispensed at baseline (270 mg (380.55)) compared to the main study cohort. Additionally, the oral route of administration was most common in those who died during the follow-up period, but not as common as it was in the main cohort (67.5% *vs*. 98.3%). Other routes of administration (intravenous, subcutaneous or intramuscular injections, buccal, rectal) were more common than in the main cohort (16.4% *vs*. 0.1%), as was the transdermal route (16.2% *vs*. 1.6%).

Description of persistent opioid users and non-persistent opioid users

A total of 11 323 (2.6%) persistent opioid users were identified (Trajectory 4 in Figure 2). All individuals who were identified as persistent users had dispensings in 7 or more months and 53.3% had dispensings in 10 or more months during the 12-month period. In total, 80.1% of persistent users did not have longer than one 3-month period without an opioid dispensing. The mean age of persistent users was 64.4 (18.3) years and 58.1% were female (Table 1). Non-persistent opioid users (n = 420 640) had a mean (SD) age of 48.0 (18.2) and 52.8% were female. Paracetamol was used by 46.6% of persistent opioid users, compared to 12.5% of non-persistent opioid users. The mean total number of comorbidities for persistent users was 5.1 (2.8) compared to 2.3 (2.0) for non-persistent users. History of depression and psychotic illness was more common among persistent opioid users than non-persistent opioid users (37.8% *vs*. 18.1%, 9.4% *vs*. 2.3%). A strong opioid was prescribed to 47.7% of persistent users at baseline and 27.4% of non-persistent users. The oral route of administration was most common (83.6% for persistent users *vs*. 98.7% for non-persistent users), followed by transdermal formulations (16.1% *vs*. 1.2%). Of the 16.1% of persistent users prescribed transdermal products at initiation, 89% of these were initiated on buprenorphine patches, while 11% were initiated on fentanyl patches. The mean (SD) total OME dispensed at baseline for persistent users was 262.4 mg (385.6) compared to 127.3 mg (172.7) in the non-persistent group. Oxycodone was the most commonly dispensed opioid (30.7%) at baseline in the persistent group, whilst paracetamol/codeine was the most commonly dispensed opioid (58.6%) in the non-persistent group.

Predictors of persistent opioid use

Predictors of persistent opioid use are shown in Table 2. The c statistic of the logistic regression model was 0.83. Compared to people aged 18–44 years, those ≥75 years were 2.5 times more likely (95% CI 2.27–2.64) to be persistent opioid users. A baseline total OME ≥ 750 mg was the strongest predictor of persistent opioid use compared to a baseline total OME >250 (OR = 3.68, 95% CI 3.34–4.06). Other predictors of persistence include being dispensed transdermal opioids (OR = 4.21, 95% CI 3.93–4.51), having depression (OR = 1.59, 95% CI 1.52–1.66), psychotic illness (OR = 2.01, 95% CI 1.87–2.17) and nicotine dependence (OR = 1.65, 95% CI 1.48–1.83). Previous use of non-opioid analgesics including NSAIDs (OR = 1.22, 95% CI 1.17–1.27), paracetamol (OR = 1.96, 95% CI 1.86–2.05) and pregabalin (OR = 1.96, 95% CI 1.83–2.10), predicted opioid persistence. Similarly, previous use of benzodiazepines (OR = 1.48, 95% CI 1.41–1.55) also predicted opioid persistence. Concessional beneficiaries were 1.9 times more likely (95% CI 1.80–2.00) to be persistent opioid users.

Sensitivity analyses

In a sensitivity analysis using an alternative definition of persistent opioid use, the predictors remained the same when compared to the main analysis (Appendix S3).

In sensitivity analyses where we stratified by age (Appendix S4), we found that the majority of the predictors of persistence were the same as the main analysis, with key differences in the strength of the prediction described below for each age sub-group.

<65 years. In the sub-group aged <65 years, baseline total OME ≥ 750 mg was the strongest predictor of persistence

Table 1

Baseline characteristics of cohort at baseline and in the 365 days prior to opioid initiation

	All (*n* = 431 963)	Non-persistent opioid users (*n* = 420 640)	Persistent opioid users (*n* = 11 323)
***n* (%) or mean ± standard deviation**			
Demographic characteristics			
Age, years	48.4 ± 18.4	48.0 ± 18.2	64.4 ± 18.3
18–44	195 859 (45.3)	193 970 (46.1)	1889 (16.7)
45–54	74 058 (17.1)	72 572 (17.3)	1486 (13.1)
55–64	67 139 (15.5)	65 283 (15.5)	1856 (16.4)
65–74	53 379 (12.4)	51 279 (12.2)	2100 (18.6)
75+	41 528 (9.6)	37 536 (8.9)	3992 (35.3)
Sex (female)	228 830 (53.0)	222 251 (52.8)	6579 (58.1)
Concessional	163 035 (37.7)	154 720 (36.8)	8315 (73.4)
Characteristics of opioid initiated			
Strong opioid	120 704 (27.9)	115 308 (27.4)	5396 (47.7)
Route			
Oral	424 444 (98.3)	414 979 (98.7)	9465 (83.6)
Transdermal	6964 (1.6)	5136 (1.2)	1828 (16.1)
Other[a]	555 (0.1)	525 (0.1)	30 (0.3)
Opioid dispensed			
Paracetamol/codeine	249 711 (57.8)	246 466 (58.6)	3245 (28.7)
Tramadol	52 656 (12.2)	50 025 (11.9)	2631 (23.2)
Buprenorphine	5872 (1.4)	4253 (1.0)	1619 (14.3)
Morphine	1380 (0.3)	1211 (0.3)	169 (1.5)
Oxycodone	112 554 (26.1)	109 081 (25.9)	3473 (30.7)
Total oral morphine equivalents (OME) in mg			
Total OME	130.8 ± 182.8	127.3 ± 172.7	262.4 ± 385.6
Total OME < 250	395 578 (91.6)	387 098 (92.0)	8480 (74.9)
Total OME 250–499	24 496 (5.7)	22 752 (5.4)	1744 (15.4)
Total OME 500–749	6840 (1.6)	6345 (1.5)	495 (4.4)
Total OME ≥ 750	5049 (1.2)	4445 (1.1)	604 (5.3)
Comorbidities[b]			
Total number	2.3 ± 2.1	2.3 ± 2.0	5.1 ± 2.8
Depression	80 429 (18.6)	76 152 (18.1)	4277 (37.8)
Psychotic illness	10 506 (2.4)	9446 (2.3)	1060 (9.4)
Alcohol dependence	803 (0.2)	763 (0.2)	40 (0.4)
Migraine	7019 (1.6)	6776 (1.6)	243 (2.2)
Nicotine dependence	10 206 (2.4)	9778 (2.3)	428 (3.8)
Prior medication use			
Benzodiazepines	54 896 (12.7)	51 701 (12.3)	3195 (28.2)
Paracetamol	57 768 (13.4)	52 496 (12.5)	5272 (46.6)
NSAIDs	118 346 (27.4)	114 268 (27.2)	4078 (36.0)

(*continues*)

Table 1

(Continued)

	All (*n* = 431 963)	Non-persistent opioid users (*n* = 420 640)	Persistent opioid users (*n* = 11 323)
Pregabalin	11 733 (2.7)	10 510 (2.5)	1223 (10.8)
Stimulants	1503 (0.4)	1473 (0.4)	30 (0.3)

NSAIDs, non-steroidal anti-inflammatory drugs
[a]Other route includes buccal, rectal and parental routes
[b]Determined by RxRisk-V and total number of comorbidities excludes the specific comorbidities listed in table

(OR = 5.97, 95% CI 5.29–6.73) and prior use of benzodiazepines (OR = 1.73, 95% CI 1.62–1.86) and pregabalin (OR 2.81, 95% CI 2.55–3.10) were stronger predictors than in the main analysis. Being male predicted persistence in the <65-year sub-group analysis (OR = 1.28, 95% CI 1.20–1.35), whilst sex did not predict persistence in the main analysis.

65–84 years. In the sub-group aged 65–84 years, being initiated on a transdermal formulation was the strongest predictor of persistence (OR = 4.24, 95% CI 3.85–4.68). Being initiated with a baseline total OME ≥ 750 mg was found to be a weaker predictor of persistence compared to the main analysis (OR = 2.20, 95% CI 1.84–2.63). Prior benzodiazepine use was also a weaker predictor of persistence compared to the main analysis (OR = 1.27, 95% CI 1.18–1.37). Being female predicted persistence (OR = 0.90, 95% CI 0.85–0.97), whilst sex did not predict persistence in the main analysis.

≥85 years. In the sub-group aged ≥85 years, being initiated on a transdermal formulation was the strongest predictor of persistence (OR = 3.47, 95% CI 3.02–3.98). Additionally, being initiated on a strong opioid was found to be a stronger predictor in this sub-analysis (OR = 1.51, 95% CI 1.32–1.73), whilst a baseline total OME ≥ 750 mg was not found to predict persistence (OR = 0.94, 95% CI 0.62–1.40). Prior benzodiazepine use was a weaker predictor of persistence compared to the main analysis (OR = 1.20, 95% CI 1.06–1.36). Being female predicted persistence (OR = 0.71, 95% CI 0.63–0.81) in this sub-analysis, whilst sex did not predict persistence in the main analysis.

Discussion

In this nationally representative cohort study of people initiating opioids in Australia, 2.6% of people without cancer were identified as persistent users during a 12-month period. Opioid initiation with a transdermal formulation and higher total OMEs strongly predicted persistent use. Patient characteristics including older age, prior history of mental health comorbidities and use of non-opioid analgesics were also found to predict persistent use of opioids. Given that long-term opioid use is associated with several harms including addiction, motor vehicle accidents, overdose and death [12], the findings from our study may be useful in guiding clinicians to better mitigate harms by identifying individuals at risk of long-term opioid use at the time of treatment initiation.

Our estimate of the percentage of people who are persistent opioid users is lower than a Canadian study where 10% of all individuals initiated on opioids for non-cancer pain in British Columbia between 2005 and 2012 were identified as long-term users (received at least 6 months of opioid therapy) [33]. Although the percentage of persistent opioid users was lower in our study, we defined persistence over a longer time period of 12 months. A Norwegian study using claims data found that 9.8% of people without cancer who were initiated on opioids were persistent opioid users using a wide definition of persistence (received a yearly total amount of opioids exceeding either 180 defined daily dose (DDD) or 4500 mg OME or both, in at least three out of four quarters of the year) [34]. Using a strict definition of persistence (received 10 or more dispensings of opioids, distributed in all quarters of the year, and receiving a total amount of opioids exceeding 730 DDDs or 18 000 mg OME per year), identified only 1.3% of opioid initiators as persistent users [34]. Our definition of persistence using GBTM avoids the need for explicit criteria to define persistence. Instead, persistence is defined by the patterns of opioid dispensings for the cohort. This was important as Svendsen *et al.* [24] found that there is no single appropriate definition for long-term opioid use when using explicit criteria.

The complex bi-directional relationship between pain and depression is well documented in the literature [33–35]. Schaakxs *et al.* [36] found that pain, based on a combination of pain intensity and pain disability experienced, was a strong risk factor for depression. Additionally, depression is associated with developing chronic pain [34]. People with chronic pain and depression report worse pain severity and functioning compared to those with either condition alone [35]. Goesling *et al.* [37] found that people with depression were equally likely to be using opioids regardless of pain severity and were more likely to take them at higher levels of functioning compared to people without depression. Our finding that people with mental health comorbidities are at greater risk of long-term opioid use are consistent with US studies [14, 15]. Hence, our study demonstrates that mental health comorbidities increase the risk of long-term opioid use and further supports current guidelines [5] recommending that clinicians should exercise additional caution and increased monitoring when prescribing opioids for people with mental health conditions. Our findings are particularly important as major depression and the use of psychotropic medication have been found to be associated

Table 2

Predictors of persistent opioid use (n = 11 323) compared to non-persistent users (n = 420 640)

	Adjusted odds ratio[a]	95% Confidence interval
Demographics		
Age (years)		
18–44	Reference	
45–54	**1.65**	**1.54–1.77**
55–64	**1.75**	**1.63–1.88**
65–74	**1.47**	**1.36–1.58**
≥75	**2.45**	**2.27–2.64**
Sex		
Male vs female	1.04	0.99–1.08
Concessional vs general status	**1.90**	**1.80–2.00**
Baseline opioid characteristics		
Strong vs weak opioid	**1.11**	**1.06–1.16**
Route		
Oral	Reference	
Transdermal	**4.21**	**3.93–4.51**
Other[b]	**0.67**	**0.46–0.97**
Total OME in mg		
<250	Reference	
250–499	**2.02**	**1.90–2.14**
500–749	**2.27**	**2.05–2.51**
≥750	**3.68**	**3.34–4.06**
Comorbidities[c]		
Total		
0	Reference	
1–2	**0.84**	**0.76–0.92**
3–4	**1.15**	**1.04–1.27**
≥5	**1.32**	**1.18–1.46**
Depression	**1.59**	**1.52–1.66**
Psychotic illness	**2.01**	**1.87–2.17**
Alcohol dependence	1.18	0.84–1.64
Migraine	1.14	0.99–1.30
Nicotine dependence	**1.65**	**1.48–1.83**
Prior medication use		
Benzodiazapines	**1.48**	**1.41–1.55**
Paracetamol	**1.96**	**1.86–2.05**
NSAIDs	**1.22**	**1.17–1.27**
Pregabalin	**1.96**	**1.83–2.10**
Stimulants	0.83	0.57–1.20

Bold values indicate statistical significance at $P < 0.05$

NSAIDs, non-steroidal anti-inflammatory drugs; OME, oral morphine equivalents.

[a]Adjusted for all the other variables listed in this table

[b]Other route includes buccal, rectal and parental routes

[c]Determined by RxRisk-V and total number of comorbidities excludes the specific comorbidities listed in table

with an increased risk of opioid misuse [38]. Additionally, Scherrer *et al*. [39] found that people who were in a period of depression remission and initiated opioids had double the risk of depression recurrence compared to those not taking opioids. Furthermore, studies in Australia have found that a history of mental health disorders is common among people who died due to prescription opioid overdose [40, 41]. Therefore, prescribers need to establish a comprehensive multimodal management plan for people with mental health comorbidities and if a trial with opioids is necessary, consider ongoing review of opioid effectiveness, dose and duration.

Use of transdermal formulations and higher total OME dispensed at baseline were both found to be strong predictors for persistent opioid use in our study. Similarly, Shah *et al*. identified that people who were initiated on higher doses of opioids were more likely to continue taking opioids for ≥1 year [13]. Although there is no ceiling dose for opioids, recommendations from recent guidelines are to start at low doses and titrate up as required to a maximum daily OME dose of 90 mg, reviewing benefit and monitoring for adverse effects at each stage [4, 42, 43]. The prescribed dose and indication for the initial opioid dispensed were not available and, therefore, it was not possible to evaluate concordance with dosing recommendations. It is possible that higher total OME may be prescribed at initiation selectively to those that have chronic pain and may therefore invoke selection bias. However, this prescribing practice is not consistent with current treatment guidelines [4, 42, 43] that suggest that if an opioid is trialled, it should be trialled at the lowest dose and for the shortest expected duration, and therefore may highlight a discrepancy between guideline recommendations and current practice. Notably, a previous study by Gadzhanova *et al*. evaluating the proportion of residents in care homes for the elderly who were opioid-naive in the 4 weeks prior to patch initiation, found that of those who were initiated on a fentanyl or buprenorphine patch, 34% and 49% were opioid naive, respectively [44]. Interestingly, in our study, opioid initiation with a transdermal formulation was found to be the strongest predictor of long-term opioid use, particularly in the 65–84-year age group. As the characteristics of the opioid initiated are selected by prescribers, our study highlights the important role of the initial opioid prescriber in contributing to the continuation of opioid use in the long term.

We found that people aged between 45 and 54 years of age were 1.7 times more likely to be persistent opioid users than those aged 18–44 years. In previous studies, younger age has been associated with opioid persistence following surgical procedures [45, 46]. Younger age has also been associated with the greatest risk of harm, particularly dependence and overdose [47, 48]. In Australia, the largest proportion of opioid overdose deaths (in those without an injecting history), occur among people aged 40–49 years [40, 41]. Although younger age has been associated with an increased risk of harm, we identified that individuals ≥75 years of age were most likely to be persistent opioid users. Similarly, a study in Germany found that those aged <40 years with CNCP had an increased risk of opioid discontinuation compared to those aged >70 years [49]. One reason for the higher rates of persistent use among older people is the higher prevalence of severe and chronic pain among people in this age group [50, 51]. Guidelines recommend more cautious prescribing of opioids in older individuals [5], as they are more susceptible to adverse events from opioids such as confusion and falls [11]. This is due to increased comorbidities and pharmacokinetic changes (e.g. reduced renal clearance) and, hence, use of lower opioid doses is recommended [5, 42]. Encouragingly, in our sub-group analyses, a baseline OME ≥ 750 mg (e.g. oxycodone 20 mg, 28 tablets) was not found to be a predictor of persistent use among those aged ≥85 years.

Concessional status (a marker of lower socioeconomic status) was also found to be a predictor of long-term opioid use. Lower socioeconomic status has previously been associated with higher opioid utilization when measured as OME per day [48]. It is possible that chronic pain is limiting working ability for people living with CNCP [52, 53]. Hence, understanding the patterns of dose escalations in those using long-term opioids may assist in identifying opioid tolerance and potential markers of problem use. Future research should also investigate the time to dose increases and progression from a weak to a strong opioid among persistent opioid users.

Strengths and limitations

A key strength of our study is that we used data from a 10% random sample of people accessing medicines through the PBS over a time period where under co-payment data was captured, therefore including the majority of opioid users in the sample. However, our study may not necessarily reflect the characteristics of all persistent prescription opioid users in Australia as non-subsidized (or private) prescriptions were not captured in this dataset. In 2011, it was estimated that private prescriptions for all medicines represented only 7.2% of community prescriptions [19], therefore it is likely that the majority of medicine dispensings were captured in our dataset. Temporary residents from 11 countries with which Australia has reciprocal health care arrangements are eligible for subsidized prescription which may lead to misclassification of these people as new opioid users or non-persistent users if they visit for a short period. However, dispensing of opioids to visitors from the 11 countries with reciprocal healthcare arrangements represents a very small percentage of PBS dispensing in Australia. Inclusion of people who died during the follow-up period would have increased misclassification of persistent users as non-persistent users. Our results indicate that those who died may have been initiated on opioids for palliative purposes, given that use of oral formulations was less common. As we used dispensing data, it is not possible to determine the cause of death for those excluded.

The c statistic (0.83) indicates that the explanatory power of our model was high. However, as this was a database study, we were unable to include predictors such as patient expectations of opioid use which has previously been found to be a strong predictor of persistence at one year [15]. We also did not have information on pain intensity, number of days with pain or the dose and indication for opioid treatment. Interestingly, Thielke *et al*. [15] found that a chronic pain prognostic risk score (calculated from baseline measures of pain intensity, pain-related interference with activities, number of days with pain in the prior 6 months and widespread pain) did not predict continuing opioid use one year after initiation. Indication for pain was also not available and, therefore, whether

certain pain types including back pain or osteoarthritis predict persistent use is unclear.

As we used dispensing data to estimate comorbidities, it is possible that some people may not be receiving pharmacological treatment for a condition or may be taking medicines for conditions not captured by the RxRisk-V tool and, therefore, we may not have identified all comorbidities. However, we used a validated tool, the RxRisk-V tool, which has been shown to predict mortality in both Australian and international studies [30, 54, 55]. Additionally, Sloan *et al*. [29] demonstrated that the RxRisk-V tool categories are stable over time and valid against international classification of diseases (ICD-9) criterion diagnoses. RxRisk-V tool has been mapped to ICD-9/10 codes and the terms used are consistent with the terminology used in these classification systems. Antipsychotic use is considered indicative of psychotic illness in the RxRisk-V tool; however, in older people this may reflect use for behavioural and psychological symptoms of dementia rather than psychotic illness. Additionally, although we used a comprehensive indicator to exclude people who have cancer, there is a possibility that some people who have cancer may not have had medicines dispensed for cancer and were therefore not captured.

Conclusion

Our study identified that 2.6% of people without cancer who initiate opioids in Australia become persistent users over a 12-month period. Mental health comorbidities, older age, prior analgesic use, initiation with transdermal formulations, strong opioids and higher total OMEs, all strongly predicted persistent opioid use. Overall, understanding the range of characteristics predicting long-term opioid use will enable prescribers to target monitoring and early intervention efforts in order to prevent future opioid-related problems developing. Future studies should explore the time to dose increases and progression from a weak to a strong opioid among persistent opioid users.

Competing Interests

There are no competing interests to declare.

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Supporting Information

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http://onlinelibrary.wiley.com/doi/10.1111/bcp.13556/suppinfo

Appendix S1 RxRisk-V categories
Appendix S2 Oral morphine equivalent (OME) conversion factors
Appendix S3 Predictors of persistent opioid use (n = 9973) compared to non-persistent users (n = 421 990) defined using an alternative definition of persistence. People who had ≤2 consecutive months without an opioid in the 12-month period were defined as persistent users
Appendix S4 Predictors of persistent opioid use stratified by age group

Appendix S1. RxRisk-V categories

Disease category	Anatomical Therapeutic Classification codes
Alcohol dependence	N07BB01-N07BB99
Allergies	R01AC01-R01AD60, R06AD02-R06AX27, R06AB04
Anticoagulation	B01AA03-B01AB06, B01AE07, B01AF01, B01AF02, B01AX05
Antiplatelet	B01AC04-B01AC30
Anxiety and tension	N05BA01-N05BA56, N05BE01
Arrhythmias	C01AA05, C01BA01-C01BD01, C07AA07
BPH	G04CA02-G04CA03, G04CB01, G04CB02, C02CA01
Bipolar disorder	N05AN01
CHF/hypertension	(C03CA01-C03CC01 AND (C09AA01-C09AA16 OR, C09CA01 - C09CX99)), C03DA04, C07AB07, C07AG02, C07AB12, C09DX04, C07AB02_02
Dementia	N06DA02-N06DA04, N06DX01
Depression	N06AA01-N06AG02, N06AX03-N06AX11, N06AX13-N06AX26
Diabetes	A10AA01-A10BX08
End-stage renal disease	B03XA01-B03XA03, V03AE02, V03AE03, V03AE05
Epilepsy	N03AA01-N03AX30
Gastric acid disorder	A02BA01-A02BX77
Glaucoma	S01EA01-S01EB03, S01EC03-S01EX02
Gout	M04AA01-M04AC01
Hepatitis B	J05AF08, J05AF10, J05AF11
Hepatitis C	J05AE11-J05AE15, J05AX14-J05AX68, J05AB04, L03AB11, L03AB60, L03AB61
HIV	J05AE01-J05AE10, J05AF01-J05AF07, J05AF09, J05AF12-J05AG05, J05AR01-J05AR19, J05AX07-J05AX09, J05AX12
Hyperkalemia	V03AE01
Hyperlipidemia	C10AA01-C10BX12
HTN	C03AA01-C03BA11, C03BB04, C03DA01-C03DA03, C03EA01-C03EA14, C09BA02-C09BA15, C09DA01-C09DA09, C02AB01-C02AC05, C02DB01-C02DB04, C03DB01-C03DB02
Hypothyroidism	H03AA01-H03AA05
IHD/angina	C01DA02-C01DA70, C01DX16, C08EX02
IHD/HTN	C07AA01-C07AA06,C07AG01, C08CA01-C08DB01, C09DB01-C09DB08, C09DX01-C09DX03, C09BB02-C09BB12, C07AB03, C07AB02_01
IBD	A07EC01-A07EC04,A07EA01-A07EA02, A07EA06, L04AA33
Liver failure	A07AA11
Malignancy	L01AA01-L01AX04, L01BA01_02, L01BA03- L01XX53, L02BG03, L02BG04, L02BG06, L02BB01-L02BB04, L02BX01-L02BX03, L04AX02, L04AX04, L04AX06, L02BA01_01, L02AE03_01, L02AE02_01
Malnutrition	B05BA01-B05BA10
Migraine	N02CA01-N02CX01
Osteoporosis/Paget's	M05BA01-M05BB08,M05BX03,M05BX04, H05AA02
Pain*	N02AA01-N02AX99, R05DA04
Pain/inflammation	M01AB01-M01AH06

Appendix S1: Continued on the next page

Disease category	Anatomical Therapeutic Classification codes
Pancreatic insufficiency	A09AA02
Parkinson's disease	N04AA01-N04BX03
Psoriasis	D05AA,D05BB01-D05BB02,D05AX02,D05AC01-D05AC51, D05AX52
Psychotic illness	N05AA01-N05AB02,N05AB06-N05AL07, N05AX01-N05AX17
Reactive airway disease	R03AC02-R03DC03, R03DX05
Nicotine dependence	N07BA01-N07BA03, N06AX12
Steroids-responsive conditions	H02AB01-H02AB17
Transplant	L04AA06, L04AA10, L04AA18, L04AD01, L04AD02, L04AC02
Tuberculosis	J04AB02, J04AC01-J04AM06

BPH, benign prostatic hypertrophy; CHF, congestive heart failure; IBD, inflammatory bowel disease; IHD, ischaemic heart disease; HIV, human immunodeficiency virus; HTN, hypertension;
*A score of 1 was deducted from the total RxRisk-V score, as the whole cohort had opioids prescribed at baseline
**Where the ATC code has _01 or_02 at the end, the ATC code could be used for multiple indications and therefore to separate indication based on PBS item codes these additional digits were used.

Appendix S2. Oral Morphine Equivalent (OME) conversion factors

Opioid name	ATC code	Route	OME factor
Buprenorphine	N02AE01	TD	15.4*
Codeine	R05DA04	O	0.1
Codeine combinations	N02AJ06	O	0.1
	N02AA59	O	0.1
Dextropropoxyphene	N02AC04	O	0.1
Fentanyl	N02AB03	TD	8.1**
Fentanyl	N02AB03	B	0.1
Hydromorphone	N02AA03	P	17.5
Hydromorphone	N02AA03	O	5
Methadone	N02AC02	P	13.6
Methadone	N02AC02	O	4.7
Morphine	N02AA01	O	1
Morphine	N02AA01	P	3
Oxycodone	N02AA05	O	1.5
Oxycodone	N02AA05	R	1.5
Oxycodone/naloxone	N02AA55	O	1.5
Pethidine	N02AB02	P	0.4
Tapentadol	N02AX06	O	0.35
Tramadol	N02AX02	P	0.3
Tramadol	N02AX02	O	0.2

ATC, Anatomical Therapeutic Chemical; B, buccal; O, oral; P, parenteral; R, rectal; TD, transdermal

*Buprenorphine OME conversion: 2.2 * 7 (1 patch lasts 7 days) = 15.4

**Fentanyl OME conversion: 2.7 * 3 (1 patch lasts 3 days) = 8.1

Appendix S3. Predictors of persistent opioid use (n=9,973) compared to non-persistent users (n=421,990) defined using an alternative definition of persistence. People who had ≤2 consecutive months without an opioid in the 12 month period were defined as persistent users.

	Adjusted Odds Ratio*	**95% Confidence Interval**
Demographics		
Age (years)		
18-44	Reference	
45-54	**1.65**	**1.53-1.77**
55-64	**1.77**	**1.64-1.90**
65-74	**1.45**	**1.34-1.57**
≥75	**2.37**	**2.19-2.57**
Sex		
Male vs female	1.02	0.97-1.06
Concessional vs general status	**1.95**	**1.84-2.06**
Baseline opioid characteristics		
Strong vs weak opioid	**1.06**	**1.01-1.11**
Route		
Oral	Reference	
Transdermal	**4.39**	**4.09-4.71**
Other**	0.69	0.46-1.04
Total OMEs in mg		
<250	Reference	
250-499	**2.08**	**1.95-2.21**
500-749	**2.39**	**2.15-2.66**
≥750	**3.67**	**3.31-4.06**
Comorbidities***		
Total		
0	Reference	
1-2	**0.86**	**0.78-0.96**
3-4	**1.17**	**1.05-1.30**
≥5	**1.31**	**1.17-1.47**
Depression	**1.57**	**1.50-1.64**
Psychotic illness	**1.99**	**1.84-2.16**
Alcohol dependence	1.13	0.79-1.62
Migraine	1.19	1.03-1.37
Nicotine dependence	**1.57**	**1.40-1.76**
Prior medication use		
Benzodiazapines	**1.46**	**1.39-1.54**
Paracetamol	**1.94**	**1.84-2.04**
NSAIDs	**1.20**	**1.15-1.26**
Pregabalin	**1.98**	**1.84-2.13**
Stimulants	0.92	0.63-1.34

Bolded values indicate statistical significance at $p < 0.05$

NSAIDs, non-steroidal anti-inflammatory drugs; OMEs, oral morphine equivalents.

*Adjusted for all the other variables listed in this table

**Other route includes buccal, rectal and parental routes

***Determined by RxRisk-V and total number of comorbidities excludes the specific comorbidities listed in table

Appendix S4. Predictors of persistent opioid use stratified by age group

Age group (total number in cohort)	**<65 years (n=337,056)**		**65-84 years (n=83,784)**		**≥85 years (n=11,123)**	
Number of persistent users (n)	n=5,231		N=4,436		n=1,656	
	Adjusted OR*	**95% CI**	**Adjusted OR***	**95% CI**	**Adjusted OR***	**95% CI**
Demographics						
Age (years)						
18-44	Reference		N/A		N/A	
45-54	**1.58**	**1.47-1.70**	N/A		N/A	
55-64	**1.65**	**1.53-1.77**	N/A		N/A	
65-74	N/A		Reference		N/A	
≥75	N/A		**1.36**	**1.27-1.45**	N/A	
Sex						
Male vs female	**1.28**	**1.20-1.35**	**0.90**	**0.85-0.97**	**0.71**	**0.63-0.81**
Concessional vs general status	**2.14**	**2.02-2.28**	**1.54**	**1.37-1.74**	0.93	0.76-1.15
Baseline opioid characteristics						
Strong vs weak opioid	1.02	0.95-1.09	1.06	0.99-1.14	**1.51**	**1.32-1.73**
Route						
Oral	Reference		Reference		Reference	
Transdermal	**3.65**	**3.15-4.21**	**4.24**	**3.85-4.68**	**3.47**	**3.02-3.98**
Other**	0.51	0.12-2.11	0.73	0.42-1.27	**0.36**	**0.21-0.64**
Total OMEs in mg						
<250	Reference		Reference		Reference	
250-499	**2.83**	**2.60-3.08**	**1.68**	**1.54-1.85**	1.16	0.98-1.37
500-749	**3.41**	**2.99-3.90**	**1.45**	**1.21-1.73**	**1.77**	**1.28-2.45**
≥750	**5.97**	**5.29-6.73**	**2.20**	**1.84-2.63**	0.94	0.62-1.40
Comorbidities* **						
Total number						
0	Reference		Reference		Reference	
1-2	**0.80**	**0.72-0.88**	0.93	0.66-1.32	1.69	0.84-3.84
3-4	**1.13**	**1.01-1.27**	1.06	0.75-1.50	**2.00**	**1.01-3.94**
≥5	**1.38**	**1.21-1.56**	1.38	0.98-1.94	1.69	0.86-3.33
Depression	**1.70**	**1.60-1.82**	**1.53**	**1.43-1.64**	**1.27**	**1.12-1.43**
Psychotic illness	**1.44**	**1.28-1.61**	**2.60**	**2.29-2.95**	**2.01**	**1.68-2.41**
Alcohol dependence	1.22	0.85-1.73	0.66	0.20-2.14	N/A	
Migraine	**1.45**	**1.24-1.71**	0.78	0.59-1.04	0.59	0.31-1.12
Nicotine dependence	**1.57**	**1.39-1.77**	**1.80**	**1.44-2.24**	1.08	0.23-5.18
Prior medication use						
Benzodiazapines	**1.73**	**1.62-1.86**	**1.27**	**1.18-1.37**	**1.20**	**1.06-1.36**
Paracetamol	**1.55**	**1.43-1.67**	**2.15**	**2.01-2.31**	**2.15**	**1.87-2.46**
NSAIDs	**1.38**	**1.30-1.46**	**1.17**	**1.10-1.25**	1.00	0.87-1.16
Pregabalin	**2.81**	**2.55-3.10**	**1.55**	**1.40-1.72**	1.18	0.95-1.47
Stimulants	0.77	0.52-1.15	0.94	0.28-3.19	N/A	

Bolded values indicate statistical significance at $p < 0.05$

CI, confidence interval; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; OMEs, oral morphine equivalents; OR, odds ratio.

*Adjusted for all the other variables listed in this table (The number of people with a history of alcohol dependence and stimulant use was too small in the ≥85 year age group, therefore not included in that model)

**Other route includes buccal, rectal and parental routes

***Determined by RxRisk-V and total number of comorbidities excludes the specific comorbidities listed in table

Chapter Five - Transition to strong or high-dose opioids: a national population-based study

Chapters Three and Four identified that 1.9 million adults initiate opioids and 2.6% (approximately 50,000 adults) become long-term opioid users in Australia. These studies did not investigate the dose or potency used after opioid initiation or their escalation to high dose or strong potency opioid. Similar to the patterns of opioid use in Chapters Three and Four, high dose opioid use has been identified as a 'problematic' pattern of opioid use by the CDC due to its association with increased harm. Currently, no studies have investigated dose escalation or use of high dose or strong potency opioids over time in Australia. Therefore, Chapter Five used Kaplan-Meier analyses to determine the cumulative percentage of individuals who escalated their opioid dose or transitioned to a strong opioid stratified by cancer status. Cox proportional hazards regression models were used to estimate hazard ratios and determine predictors of these transitions.

This chapter is a reproduction of the following manuscript submitted to Addiction:

Lalic S, Gisev N, Bell JS, Ilomäki J. Transition to high-dose or strong opioids: a population-based study of people initiating opioids in Australia. Addiction. 2019; revised October.

5.0 Abstract

Background and aims: Strong and high-dose opioids are associated with opioid overdose and death. The objective of this study was to determine the rate and predictors of transitioning to high-dose or strong opioids among people initiating opioids.

Design: Retrospective cohort study.

Setting: Australia.

Participants: People initiating opioid analgesics from July 2013 to January 2018 were identified from a random 10% sample of Australia's Pharmaceutical Benefits Scheme eligible population.

Measurements: Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the predictors of escalating to ≥50 mg Oral Morphine Equivalents (OMEs)/day (Cohort 1); ≥90 mg OMEs/day (Cohort 2) and transitioning from weak opioids to strong opioids (Cohort 3) over 12-months of follow-up. Predictors included age, sex, number of comorbidities, history of depression, prior treatment for cancer, and selected other medication use.

Findings: In total, 861,691 people initiated opioids at average doses <50mg OMEs/day (Cohort 1), 874,401 at <90mg OMEs/day (Cohort 2) and 603,884 initiated weak opioids (Cohort 3). Overall, 1.4% of people escalated to doses ≥50mg OMEs/day, 0.8% to doses ≥90mg OMEs/day, and 7.3% transitioned to strong opioids. The strongest predictors of transitioning included prior treatment for cancer (Cohort 1:HR=3.19, 95%CI 3.00-3.40; Cohort 2:HR=4.19, 95%CI 3.90-4.51; Cohort 3:HR=2.07, 95%CI 1.95-2.18) and age ≥75 years (Cohort 1:HR=3.04, 95%CI 2.73-3.38, Cohort 2:HR=2.51, 95%CI 2.17-2.89; Cohort 3:HR=1.88, 95%CI 1.80-1.96). Females transitioned less rapidly (Cohort 1:HR=0.79, 95%CI 0.76-0.82; Cohort 2:HR=0.70, 95%CI 0.66-0.73; Cohort 3:HR=0.95, 95%CI 0.93-0.96).

Conclusions: More than one in every 13 people initiating weak opioids transition to strong opioids. By extrapolation, our results suggest >26,000 Australian adults initiating opioids escalate to high-doses each year. People with cancer treatment history, older people and males transition to strong and high-dose opioids more rapidly.

5.1 Introduction

More than 17,000 overdose deaths involved prescription opioids in the United States in 2016.[245] There were 3,998 overdose deaths involving prescribed and illicit opioids in Canada in 2017,[184] and 679 overdose deaths involving opioid analgesics in Australia in 2016.[187] The majority of these overdose deaths were unintentional.[184, 187, 245] Increases in overdose deaths have been linked to increases in opioid use for chronic non-cancer pain (CNCP).[17, 105, 246, 247] Although the prevalence of opioid use has stabilized in North America and Australia since 2012,[57, 105, 248] there is ongoing concern about high-dose opioid use.[119] The average daily dose in the US declined from 58 mg oral morphine equivalents (OMEs)/day in 2010 to 48 mg OMEs/day in 2015, but the dispensed OMEs per person remained six times higher in the highest-prescribing counties than in the lowest-prescribing counties.[245] Prescribing of high-dose opioids (>200 mg OMEs/day) doubled from 4.2% in 2003 to 8.7% in 2014 in Ontario, Canada.[118] The incidence of opioid use slightly declined from 2013 to 2017 in Australia but initiation of strong opioids increased over this period.[105] Of the 1.9 million adults who initiate opioids each year in Australia,[105] nearly 50,000 will become persistent users.[244] It is unclear how many of these people escalate to high-doses or transition to strong opioids.

High-dose opioid use is associated with falls, fractures, hospitalization, motor vehicle injury and opioid-related overdose and death.[14, 15, 116-118, 127, 249] Definitions of high-dose opioid use vary (range 50-200 mg OMEs/day).[14, 15, 116-119, 127, 249] An average dose of ≥50 mg OMEs/day has been associated with double the risk of overdose compared to 20 mg OMEs/day.[127, 250] Moreover, an average dose of ≥90 mg OMEs/day was associated with 4-10 times greater risk of overdose compared to 20 mg OMEs/day.[15, 127, 250] The Centres for Disease Control and Prevention (CDC) and Canadian guidelines recommend avoiding doses ≥90 mg OMEs/day.[28, 29] Despite evidence of harm,[26] a retrospective cohort study in the US found 9% of people initiating opioids escalated their daily dose (defined as an increase of ≥30 mg OMEs) over a year.[114] A Canadian study found males were at higher risk than females to escalate to high-doses and experience opioid-related overdose deaths.[251] No Australian studies have investigated escalation to high-doses or transition

from weak to strong opioids. The objective of this study was to determine the rate and predictors of transitioning to high-dose or strong opioids among people initiating opioids.

5.2 Methods

5.2.1 Study design and setting

We conducted a retrospective population-based cohort study of people who initiated prescription opioid analgesics in Australia between July 2013 and January 2018. Data from a random 10% sample of people eligible for Australia's Pharmaceutical Benefits Scheme (PBS) were used. The PBS subsidizes prescriptions for Australian citizens, permanent residents and foreign visitors from countries with reciprocal health care agreements.[252] This sample is considered representative of medication dispensing for the 25 million people in Australia.[253] The PBS data were sourced from the Australian Government Department of Human Services. The PBS subsidizes prescriptions for Australian citizens, permanent residents and foreign visitors from countries with reciprocal health care agreements. Each year two co-payment thresholds are set: a general co-payment amount and a concessional co-payment amount. Prior to July 2012 medications that cost less than the general co-payment amount were not recorded in the PBS dataset for general beneficiaries.[252] Since this time, data for all dispensed medications, including those that cost less than the general co-payment amount have been included.[252] Concessional beneficiaries (e.g. pensioners and those earning a low income) pay the lower concessional co-payment amount. Information regarding medications dispensed (PBS item number specific to medication name and strength, quantity and date dispensed), demographic information (sex, year of birth, and year of death), beneficiary status (concessional or general), and prescriber specialty are recorded in the PBS dataset. Medications were categorized according to the World Health Organization's (WHOs) Anatomical Therapeutic Chemical (ATC) classification system.[254] In 2014 it was estimated that PBS data captured 80% of all prescription opioids used in Australia.[230]

5.2.2 Study population

We included adults aged 18-99 years who initiated opioids between 1st July 2013 and 31st of January 2018. People aged ≥100 years were excluded to ensure anonymity. Non-recent users were defined as those with no opioid dispensings in the 12 months prior to the initial opioid dispensing. People could be included as non-recent users on multiple occasions throughout the study period if they re-initiated opioids after no opioid dispensings for 12 months.

Three study cohorts were formed (Figure 2). Cohort 1 included people initiated on an average dose of <50mg OMEs/day in the first month of opioid initiation. Cohort 2 included people initiated on an average dose of <90mg OMEs/day in the first month of opioid initiation. As a consequence of the threshold definition, Cohort 1 is a subset of Cohort 2. Compared with lower dosages, doses ≥50mg and ≥90 mg OMEs/day increase the risk of overdose by up to 2-10-fold.[15, 127, 250] The US[29] and Canadian[28] guidelines for prescribing in CNCP suggest that clinicians should carefully reassess evidence of individual benefits and risks when considering increasing dosage ≥50mg OMEs/day. Additionally, these guidelines suggest that increasing dosage to ≥90 mg OMEs/day should be avoided or the decision to titrate dosage to ≥90 mg OMEs/day should be carefully justified.[28, 29] The thresholds chosen in this study reflect the recommendations from clinical practice guidelines based on evidence on overall risk vs benefit. Cohort 3 included people initiated on a weak opioid only. Opioids were categorized as weak or strong based on relative potencies (Appendix 1).[255] People dispensed both weak and strong opioids on the date of initiation were categorized as strong opioid initiators and were excluded from the Cohort 3 analysis.

5.2.3 Average OMEs/day calculation

To estimate the average dose in OMEs/day for individuals, the total OMEs dispensed for each 30 day period were calculated and divided by 30. This approach was consistent with previous international studies and no assumptions were made about the intended treatment duration.[14, 256, 257] The OMEs for each dispensing was calculated using the formula: *(pack strength * OME conversion factor of opioid dispensed * quantity dispensed)* and then summed to get the total OMEs in each 30 day period. Well-established OMEs conversion factors were used.[91]

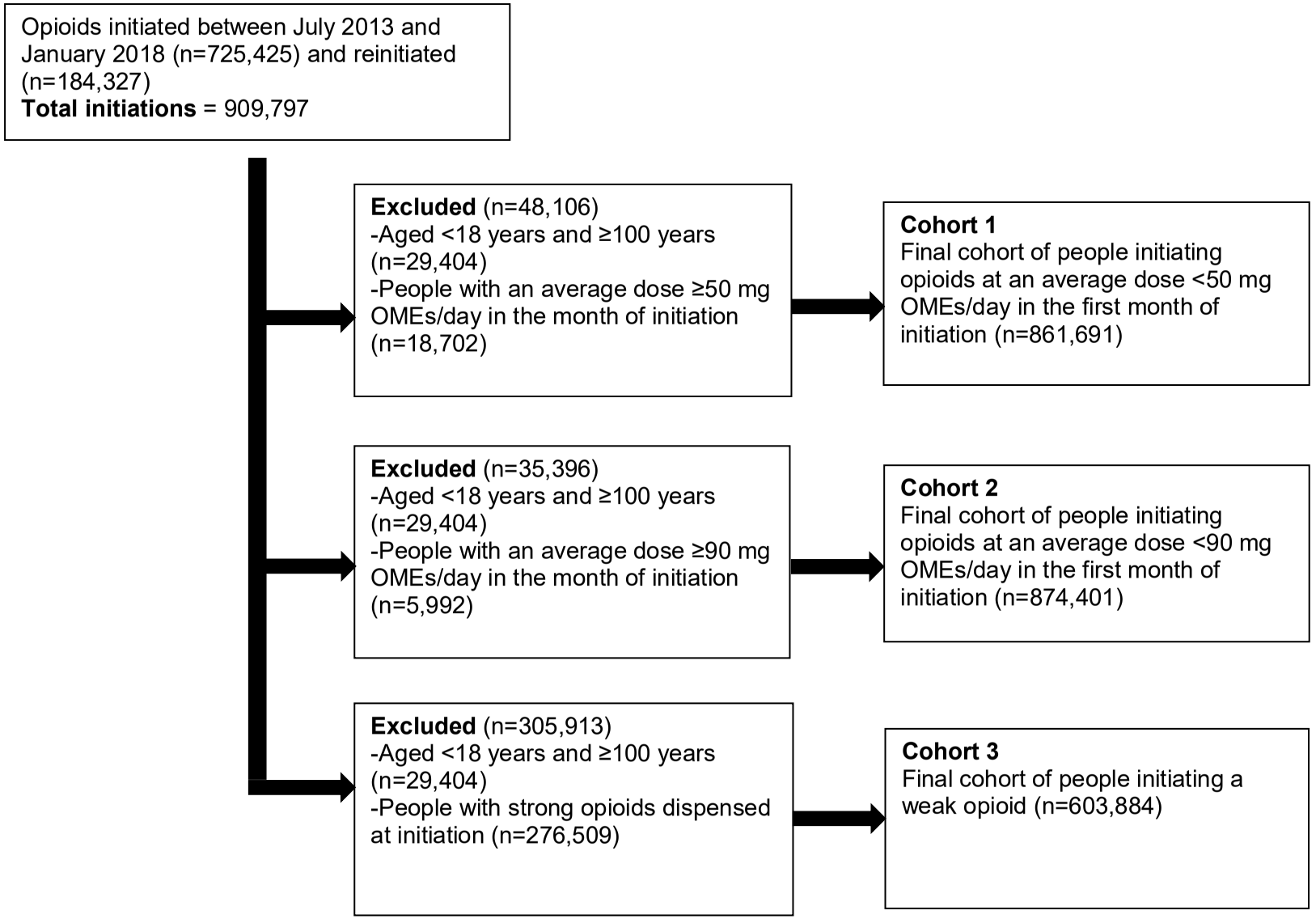

Figure 2. Flow diagram of study populations for the three cohorts investigated.

5.2.4 Previous medication use

We investigated previous benzodiazepine (Appendix 1, ATC code N05BA,N05CD) use as a predictor because benzodiazepines have been implicated in opioid-related overdose deaths.[124] We also considered non-opioid analgesic use which included: paracetamol (N02BE01), pregabalin (N03AX16) and non-steroidal anti-inflammatory drugs (NSAIDs) (M01AB01-M01AH06). NSAIDs were further categorized into non-selective NSAIDs and COX-2 selective (Appendix). To reflect recent treatment, previous medication use was defined as any dispensing three months prior to or on the date of opioid initiation.

5.2.5 Medical conditions

Comorbidities were determined using the validated RxRisk-V tool which uses records of dispensed medications to identify probable medical conditions.[258] A look-back period of 12-months from the date of opioid initiation was used to establish likely comorbidities. The total number of comorbidities was calculated using the sum of comorbidities excluding prior treatment of cancer, depression, anxiety, and pain. These comorbidities were analyzed separately due to their potential to influence transition to high dose or strong opioids. Pain as a comorbidity using the RxRisk-V tool is determined by the presence of an opioid dispensing while pain/inflammation is determined by the presence of dispensings for NSAIDs. As all individuals had an opioid dispensed on initiation, opioid use (i.e. pain as a comorbidity) was not included in the total number of comorbidities and prior use of NSAIDs was investigated separately. The total number of comorbidities was modelled as a continuous variable. Previous Australian research has indicated that the RxRisk-V tool identifies fewer people with cancer compared to the Charlson's Comorbidity Index (43.2% vs 67.2%) which is a widely used and considered a 'gold standard' approach to assess disease burden [259] For this reason we used a more comprehensive medication-based indicator of cancer treatment that included other antineoplastic therapies such as hormonal cancer therapies.[105, 244] Cancer treatment history was used as a predictor because cancer-related pain could influence the rate of opioid transitions. Other comorbidities including

depression and anxiety were also investigated as predictors separately because the prevalence of opioid-related harm is higher among people with mental health disorders.[260]

5.2.6 Outcome definition

The outcomes of interest were: an average dose escalation to ≥50 mg OMEs/day (Cohort 1), an average dose escalation to ≥90 mg OMEs/day (Cohort 2), and transition from a weak to a strong opioid (Cohort 3) during the 12-month follow-up. Since the average daily dose was estimated over each month during follow-up, the outcome for Cohorts 1 and 2 were measured at each 30-day period following the date of initiation.

5.2.7 Statistical analyses

Baseline characteristics of the cohort were described using frequencies, percentages, medians and interquartile ranges (IQRs). Poisson regression was used to calculate the rate ratios (RRs) for transitioning to strong or high-dose opioids. Unadjusted Kaplan-Meier analyses were used to determine the cumulative percentage of individuals who escalated their opioid dose (model for Cohorts 1 and 2) or transitioned to a strong opioid (model for Cohort 3), stratified by cancer treatment history because baseline cancer-related pain could influence the rate of opioid transitions. Cox proportional hazards regression was used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for the predictors of time to first high-dose escalation and the time to transition to a strong opioid. Participants were censored at opioid discontinuation, date of death (based on the last month of dispensing and year of death) or study end date, whichever occurred first. Opioid discontinuation was defined as three consecutive months without an opioid dispensing. The discontinuation date was defined as the end of the third clear month without an opioid dispensing. Predictors in multivariable models included age, sex, number of comorbidities, history of depression and selected prior medication use. The percentage of people that had a new comorbidity in the follow-up period was 0.90% (n=5,408) for Cohort 1, 1.39% (n=11,991) for Cohort 2 and 1.49% (n=13,012) for Cohort 3. Because the percentages were minimal, we did not consider time-varying covariates in our models. To determine the effect

of including people who reinitiate opioids on the predictors of dose escalation and transition from weak to strong opioids, sensitivity analyses were conducted excluding people who reinitiated opioids over the study period (Cohort 1: n=174,634, 20.3%; Cohort 2: n=178,921, 20.5%; Cohort 3: n=96,511, 16.0%; Figure 1). The new cohorts consisted of 687,057 people (Cohort 1), 695,480 people (Cohort 2) and 507,373 people (Cohort 3). For all three cohorts, the majority of people (90%) who reinitiated only reinitiated once. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

5.2.8 Ethics and analysis approval

The study was approved by the Monash University Human Research Ethics Committee. The analysis plan was approved by the Australian Government Department of Human Services (DHS). The manuscript was noted by the External Request Evaluation Committee which is chaired by the DHS.

5.3 Results

There were 861,691 people who initiated on an average dose of <50 mg OMEs/day (Cohort 1), 874,401 who initiated on an average dose of <90 mg OMEs/day (Cohort 2) and 603,884 people who initiated weak opioids only (Cohort 3) (Table 6, 7).

Table 6. Baseline characteristics of each study cohort.

	Cohort 1 Initiated on <50mg OMEs/day[1] (n=861,691)	Cohort 2 Initiated on <90mg OMEs/day[1] (n=874,401)	Cohort 3 Initiated on weak opioid (n=603,884)
N(%) or median (interquartile range)			
Demographic characteristics			
Age, years	48(34-64)	48(34-64)	46(33-61)
18-29	154,055(17.9)	154,719(17.7)	115,711(19.2)
30-44	224,130(26.0)	225,865(25.8)	165,648(27.4)
45-54	144,396(16.8)	146,172(16.7)	106,124(17.6)
55-64	133,415(15.5)	135,815(15.5)	93,423(15.5)
65-74	110,016(12.8)	112,847(12.9)	72,463(12.0)
75+	95,679(11.1)	98,983(11.3)	50,515(8.4)
Sex, female	458,883(53.3)	464,812(53.2)	318,647(52.8)
Concessional beneficiary	329,898(38.3)	337,404(38.6)	224,948(37.3)
Comorbidities*			
Total number**	2(1-4)	2(1-4)	2(1-3)
Alcohol dependence	1,683(0.2)	1,719(0.2)	1,196(0.2)
Depression	167,083(19.4)	170,838(19.5)	112,802(18.7)
Nicotine dependence	18,993(2.2)	19,374(2.2)	14,036(2.3)
Psychotic illness	23,779(2.8)	24,508(2.8)	14,150(2.3)
Benzodiazepines* **	65,875(7.6)	67,827(7.8)	43,204(7.2)
Alprazolam	1,897(0.2)	1,970(0.2)	1,284(0.2)
Diazepam	33,254(3.9)	34,148(3.9)	23,366(3.9)
Nitrazepam	1,929)(0.2)	1,999(0.2)	1,294(0.2)
Oxazepam	7,941(0.9)	8,231(0.9)	4,407(0.7)
Temazepam	25,278(2.9)	26,096(3.0)	15,631(2.6)
Non-opioid analgesics* **	232,191(27.0)	238,521(27.3)	145,175(24.0)
Paracetamol	65,946(7.7)	69,482(8.0)	30,876(5.1)
Pregabalin	22,463(2.6)	23,598(2.7)	13,010(2.2)
NSAIDs	173,090(20.1)	176,480(20.2)	116,633(19.3)
Selective COX-2 inhibitors	83,417(9.7)	85,383(9.8)	54,342(9.0)
Meloxicam	45,392(5.3)	46,507(5.3)	31,282(5.2)
Celecoxib	39,414(4.6)	40,319(4.6)	23,912(4.0)
Nonselective NSAIDs	94,740(11.0)	96,286(11.0)	65,594(10.9)
Diclofenac	33,476(3.9)	33,984(3.9)	22,818(3.8)
Ibuprofen	29,756(3.5)	30,169(3.5)	20,223(3.4)
Naproxen	19,641(2.3)	20,012(2.3)	14,208(2.4)
Indometacin	9,179(1.1)	9,389(1.2)	6,198(1.0)
Piroxicam	2,332(0.3)	2,388(0.3)	1,801(0.3)
Mefanamic acid	1,314(0.2)	1,327(0.2)	1,002(0.2)
Ketoprofen	1,093(0.1)	1,127(0.1)	752(0.1)

Cyclooxygenase-2 (COX-2); Non-steroidal anti-inflammatory drugs (NSAIDs); Oral Morphine Equivalents (OMEs).

1 Calculated as an average dose per day in the first month of opioid initiation.

*Determined by RxRisk-V at baseline and in the 12-months prior to opioid initiation. RxRisk-V uses records of dispensed medications to identify probable medical conditions.

** Total number excludes cancer treatment history, opioid and NSAID treated pain, anxiety and depression treatment history.

***Medication of interest determined at baseline and in the 3-months prior to opioid initiation.

Table 7. Characteristics of opioids dispensed on the date of initiation for each study cohort.

	Cohort 1 Initiated on <50mg OMEs/day[1] (n=861,691)	Cohort 2 Initiated on <90mg OMEs/day[1] (n=874,401)	Cohort 3 Initiated on weak opioid (n=603,884)
N(%) or median (interquartile range)			
Type of opioid			
Weak opioid	597,673(69.4)	602,038(68.9)	603,884(100)
Strong opioid	244,621(28.4)	251,972(28.8)	0(0.0)
Both weak and strong opioid	19,397(2.3)	20,391(2.3)	0(0.0)
Short-acting	765,647(88.9)	770,308(88.1)	571,886(94.7)
Long-acting	69,398(8.1)	74,173(8.5)	29,099(4.8)
Both short- and long-acting	26,646(3.1)	29,920(3.4)	2,899(0.5)
Route of administration			
Oral	842,870(97.8)	854,175(97.7)	603,749(100)
Transdermal	12,979(1.5)	13,921(1.6)	0(0)
Other	3,986(0.5)	4,108(0.5)	116(0.0)
≥Two routes	1,856(0.2)	2,197(0.3)	<30(0.0)
Opioid dispensed			
Buprenorphine	12,744(1.5)	13,438(1.5)	0(0.0)
Codeine	39,363(4.6)	39,412(4.5)	39,298(6.5)
Fentanyl	1,718(0.2)	2,247(0.3)	0(0.0)
Hydromorphone	653(0.1)	958(0.1)	0(0.0)
Morphine	6915(0.8)	7,511(0.9)	0(0.0)
Paracetamol/codeine	475,113(55.1)	476,401(54.5)	465,609(77.1)
Oxycodone	215,247(25.0)	220,304(25.2)	0(0.0)
Oxycodone/Naloxone	44,243(5.1)	47,532(5.4)	0(0.0)
Tapentadol	6,471(0.8)	7,285(0.8)	6,555(1.1)
Tramadol	100,468(11.7)	103,839(11.9)	96,660(16.0)
Average oral morphine equivalents (OMEs) in milligrams per day*			
OMEs	4.0(2.0-6.7)	4(2-6.7)	2(2-4)
OMEs <10	702,010(81.5)	702,010(80.3)	537,251(89.0)
OMEs 10-19	102,163(11.9)	102,163(11.7)	37,133(6.2)
OMEs 20-49	57,518(6.7)	57,518(6.6)	23,289(3.9)
OMEs 50-89	0(0.0)	12,710(1.5)	4,365(0.7)
OMEs ≥90	0(0.0)	(0.0)	1,846(0.3)
Prescribed by general practitioner	368,516(42.8)	374,477(42.8)	305,026(50.5)

[1] Calculated as an average dose per day in the first month of opioid initiation

Figure 3 a-c shows the unadjusted Kaplan Meier curves for Cohorts 1-3 describing the time to dose escalation ≥50 mg OMEs/day, the time to dose escalation ≥90 mg OMEs/day, and the time to transition to strong opioids.

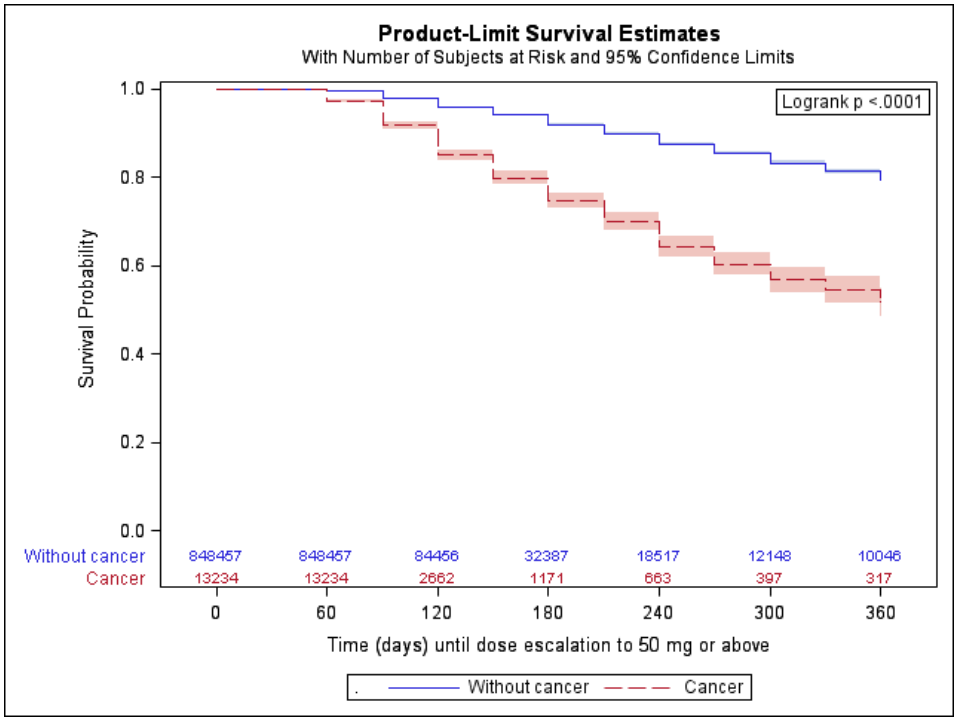

Figure 3a. Unadjusted Kaplan Meier survival curve for time in days until dose escalation to ≥50 mg oral morphine equivalents (OMEs)/day stratified by cancer treatment history determined at baseline or in the 12-months prior to opioid initiation.

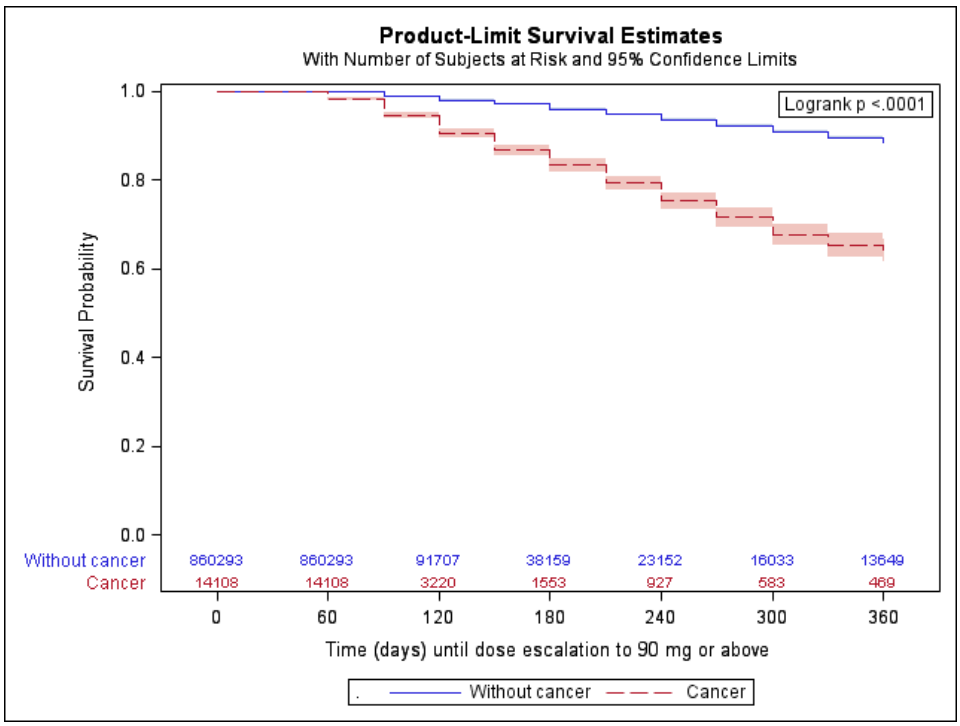

Figure 3b. Unadjusted Kaplan Meier survival curve for time in days until dose escalation to ≥90 mg OMEs/day stratified by cancer treatment history determined at baseline or in the 12-months prior to opioid initiation.

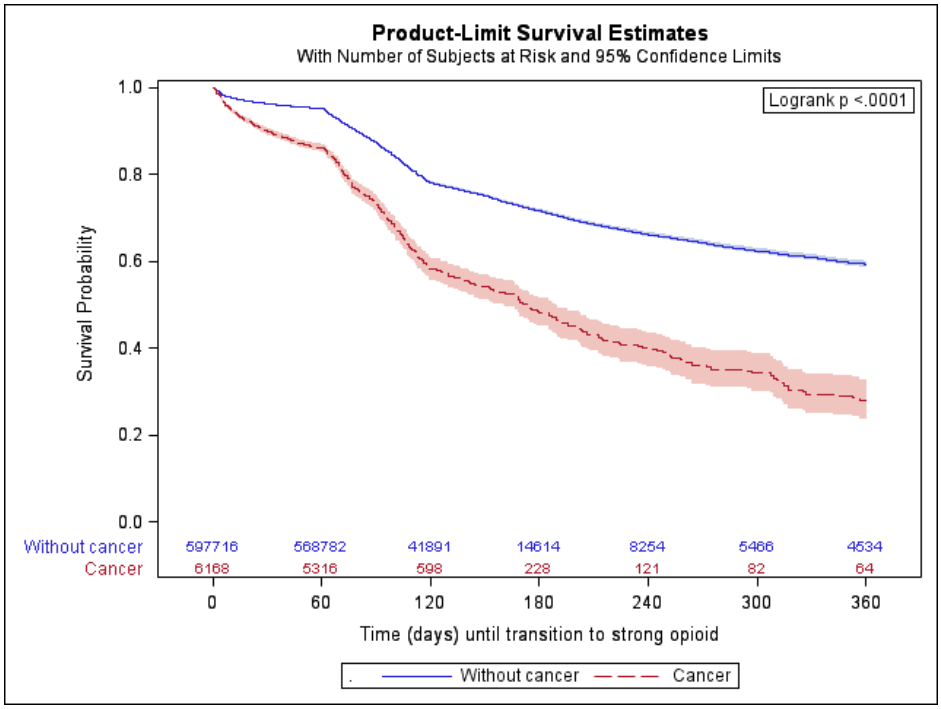

Figure 3c. Unadjusted Kaplan Meier survival curve for time in days until transition from a weak opioid to a strong opioid stratified by cancer treatment history determined at baseline or in the 12-months prior to opioid initiation.

The rate of dose escalation to ≥50 mg OMEs/day was 6.7/100 person-years (95%CI 6.6-6.9) and 3.7/100 person-years (95%CI 3.7-3.8) for escalation to ≥90 mg OMEs/day (Table 8). The rate of strong opioid transition was 39.4/100 person-years (95%CI 39.0-39.8). Among people with a dose escalation, the median time to escalate to ≥50 mg OMEs/day was 120 days (IQR 60-180) and to ≥90 mg OMEs/day was 120 days (IQR 90-120). Of those that transitioned from weak to strong opioids, the median time to transition was 29 days (IQR 7-76).

Table 8. Incidence rates for dose escalation to ≥50 mg oral morphine equivalents (OMEs)/day (cohort 1); dose escalation to ≥90 mg OMEs/day (cohort 2), or transition from weak to strong opioids (cohort 3).

	Cohort 1 initiated on <50mg OMEs/day[1] (n=861,691)	Cohort 2 Initiated on <90mg OMEs/day[1] (n=874,401)	Cohort 3 initiated on weak opioids (n=603,884)
People with cancer treatment history			
Number of people who transition	1,141	902	1,295
Person years	3,204	3,628	1,167
Rate per 100 person years (95% CI)	35.6 (33.6-37.7)	24.9 (23.3-26.5)	111.0 (105.1-117.2)
People without no cancer treatment history			
Number of people who transition	10,574	5,866	42,853
Person years	170,962	177,276	110,881
Rate per 100 person years (95% CI)	6.2 (6.1-6.3)	3.3 (3.2-3.4)	38.7 (38.3-39.0)-
Whole cohort			
Number of people who transition	11,715	6,768	44,148
Person years	174,167	180,904	112,048
Rate per 100 person years (95% CI)	6.7 (6.6-6.9)	3.7 (3.7-3.8)	39.4 (39.0-39.8)

Predictors of dose escalation to ≥50 mg and ≥90 mg OMEs/day

The predictors and HRs were similar across all three models (Table 4). The hazard of dose escalation to ≥50 mg OMEs/day was highest among people aged ≥75 years compared to those aged 18-29 years (HR=3.04, 95% CI 2.73-3.38). The hazard of dose escalation to ≥90 mg OMEs/day was highest among people aged 45-54 years and 55-64 years compared to those aged 18-29 years (HR=2.79, 95% CI 2.43-3.19; HR=2.81, 95% CI 2.44-3.19, respectively). People with cancer treatment history escalated to high-doses more rapidly than people with no prior cancer treatment history (Cohort 1: HR=3.19, 95% CI 3.00-3.40; Cohort 2: HR=4.19, 95% CI 3.90-4.51). Females escalated to high-doses less rapidly than males (Cohort 1: HR=0.79, 95% CI 0.76-0.82; Cohort 2: HR=0.70, 95% CI 0.66-0.73).

Predictors of transition from weak to strong opioid

The hazard of transitioning to strong opioids was highest among people aged ≥75 years compared to those aged 18-29 years (HR=1.88, 95% CI 1.80-1.96) (Table 4). People with prior cancer treatment history transitioned more rapidly than people with no prior cancer treatment history (HR=2.07, 95% CI 1.95-2.18). Females transitioned less rapidly to strong opioids than males (HR=0.95, 95% CI 0.93-0.96).

Sensitivity analyses

In the sensitivity analyses excluding people who reinitiated opioids over the study period (Appendix 2), the predictors and HRs in the adjusted analyses were similar to the main adjusted analyses for all three cohorts.

Table 9. Predictors of time to first dose escalation to ≥50 mg oral morphine equivalents (OMEs) per day (cohort 1); time to first dose escalation to ≥90 mg OMEs per day (cohort 2), or time to first transition from weak opioids to strong opioids (cohort 3).

	Cohort 1 initiated on <50mg OMEs/day[1] (n=861,691)	Cohort 2 Initiated on <90mg OMEs/day[1] (n=874,401)	Cohort 3 initiated on weak opioids (n=603,884)
Hazard Ratio (95% Confidence Intervals)			
Demographic characteristics			
Age, years			
18-29	Reference	Reference	Reference
30-44	1.59(1.43-1.77)	1.65(1.43-1.90)	1.10(1.07-1.14)
45-54	2.28(2.05-2.53)	2.40(2.09-2.76)	1.14(1.10-1.19)
55-64	2.90(2.62-3.21)	2.79(2.43-3.19)	1.24(1.19-1.28)
65-74	2.92(2.63-3.24)	2.81(2.44-3.19)	1.49(1.44-1.55)
≥75	3.04(2.73-3.38)	2.51(2.17-2.89)	1.88(1.80-1.96)
Sex, female	0.79(0.76-0.82)	0.70(0.66-0.73)	0.95(0.93-0.96)
Concessional beneficiary	1.20(1.15-1.26)	1.19(1.12-1.27)	0.89(0.87-0.91)
Comorbidities*			
Total number**	1.02(1.01-1.03)	1.01(1.00-1.02) p=0.0431	1.03(1.03-1.04)
Cancer treatment history	3.19(3.00-3.40)	4.19(3.90-4.51)	2.07(1.95-2.18)
Depression	1.19(1.14-1.24)	1.17(1.11-1.24)	1.18(1.15-1.21)
Prior use of selected medication in the past 3 months			
Benzodiazepines	1.20(1.14-1.26)	1.22(1.15-1.31)	1.19(1.15-1.23)
Paracetamol	1.20(1.14-1.25)	1.12(1.05-1.19) p=0.0007	1.08(1.04-1.11)
Pregabalin	1.63(1.53-1.73)	1.56(1.44-1.69)	1.35(1.29-1.41)
NSAIDs	1.16(1.11-1.21)	1.05(1.00-1.12) p=0.0701	1.25(1.22-1.28)
Prescriber, general practitioner	1.10(1.06-1.14)	1.03(0.98-1.08) p=0.2328	0.94(0.92-0.96)

Cox proportional hazard models were used to estimate the hazard ratios. The model was adjusted for all variables in the table. All p values were <0.0001, except where specified.
[1]Calculated as an average dose per day in the first month of opioid initiation.
*Determined by RxRisk-V at baseline and in the 12-months prior to opioid initiation. RxRisk-V uses records of dispensed medications to identify probable medical conditions.
** Total number excludes cancer treatment history, opioid and NSAID treated pain, anxiety and depression treatment history.

5.4 Discussion

This is the first population-based cohort study to evaluate high-dose escalation and transition to strong opioids in Australia. Our study found that 7.3% of people who initiated weak opioids transitioned to strong opioids over a 12-month period. Additionally, 1.4% of people escalated to doses ≥50 mg OMEs/day and 0.8% of people to doses ≥90 mg OMEs/day. People with cancer treatment history, men and people aged ≥75 years transitioned more rapidly to strong and high-dose opioids.

Our results have clinical practice and policy implications because high-doses have been associated with substantial morbidity and mortality, including, falls, fractures, hospitalization, motor vehicle accidents and opioid-related overdose and death.[14, 15, 116-118] A recent Australian study reported 1.9 million people initiate opioids each year.[105] By extrapolation, approximately 26,600 people who initiate opioids escalate to high-doses over 12-months. A CDC report published in 2017 reported five prescriptions per 100 persons in the US were for high-dose opioids (≥90 mg OMEs/day).[245] Clinician education and policies limiting doses and repeat prescriptions may reduce the risk of inappropriate dose escalation including escalations that are too rapid or escalations to higher than appropriate doses.[261, 262]

Older people and males more rapidly escalated to high-dose opioids. People aged ≥75 years escalated to doses ≥50 mg OMEs/day most rapidly and people aged 65-74 years escalated to doses ≥90 mg OMEs/day most rapidly. These findings are important because age-related pharmacokinetic and pharmacodynamics changes[263, 264] mean older people are more susceptible to opioid-related adverse events, such as drowsiness, falls[201] and delirium.[264] Research has shown that there is a 50% increase in brain sensitivity to opioids from ages 20 to 89.[265] High-dose opioid use (≥50 mg OMEs) has also been associated with a 10% annual fracture rate among people aged ≥60 years.[117] Current US guidelines recommend cautious prescribing for people aged ≥65.[29] Our study highlights the need to consider age-related adverse events if dose escalation is considered in CNCP management. Our finding that males were at greater risk of

high-dose opioid escalation was similar to that of a retrospective cohort study in Ontario, Canada.[251] This study found that males prescribed opioids for CNCP were at higher risk than females to escalate to high-doses and experience overdose deaths.[251] This is interesting because more females initiated opioids than males in our study. These findings may suggest a need for greater public and health professional awareness of potential opioid-related harm, particularly among males and older people.

Prior cancer treatment history was a strong predictor of dose escalation and transition to strong opioids. This was consistent with the knowledge that people with cancer pain often escalate to higher opioid doses to maintain effective analgesia.[22] The need for higher doses and strong opioids may be due to disease progression, development of opioid tolerance and psychological factors including distress.[266] WHO's analgesic ladder recommends using weak opioids prior to strong opioids for cancer pain.[22] However, this recommendation has been challenged by results of a recent randomized controlled trial that found in adults with moderate cancer pain, low-dose morphine reduced pain intensity, had similar tolerability and faster onset of action compared with weak opioids.[1] Among those who transition to a strong opioid, the median time to transition was one month. There is insufficient evidence suggesting whether initiation with a weak or strong opioid is most beneficial. However, WHO's analgesic ladder has been widely adopted in clinical practice, although modifications have been proposed including immediate initiation at step 3 (strong opioid) for intense pain.[267]

5.4.1 Strengths and limitations

This population-based study used administrative claims data from a 10% random sample of Australians eligible for dispensing of medication through the PBS. A key strength is that we analyzed data over a period where under co-payment data were recorded, ensuring complete capture of PBS-listed opioid dispensings. Data on non-subsidized prescriptions, non-prescription medications or inpatient hospital dispensings were not captured. This means paracetamol and NSAIDs purchased without a prescription were not captured. Additionally, the PBS subsidy of

paracetamol changed throughout the study period. Since January 2016, paracetamol has no longer been subsidized on the PBS. This means that we may have underestimated prior paracetamol and NSAID use. Additionally, records of outpatient dispensings from hospitals in New South Wales and Australian Capital Territory were not recorded. However, it has been estimated that PBS data now capture more than 80% of prescription opioid use in Australia.[230] In the absence of data on actual individual comorbidities, we used a comprehensive medication-based indicator to determine a range of likely comorbidities for the cohort. Although we used a published list of anticancer medications and included hormonal anticancer therapies to determine likelihood of treatment for cancer, it is possible that some people with cancer may not have had anticancer medications dispensed on the PBS (or at all) and therefore may have been misclassified as having no cancer treatment history. We used a method for defining opioid dose that was consistent with previous studies.[118, 268] It is possible that the actual dose for individual patient's was different to the calculated average daily dose. PBS dispensing data do not include information on pain severity or the indication for opioid treatment. However, a recent review suggests that functional outcomes rather than pain severity should guide prescribing decisions for the management of CNCP.[65] We did not have information on functional outcomes.

5.5 Conclusion

More than one in every 13 people initiating weak opioids transition to strong opioids. By extrapolation, our results suggest >26,000 Australian adults initiating opioids escalate to high-doses each year. People with cancer treatment history, older people and males transition to strong and high-dose opioids more rapidly.

5.6 Acknowledgement

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Appendix 1. Name of medicines used in analyses and their corresponding Anatomical Therapeutic Classification codes[254]

Medicine Name	Anatomical Therapeutic Classification codes
Paracetamol	N02BE01
Pregabalin	N03AX16
NSAIDs	M01AB01-M01AH06
Nonselective	
• Diclofenac	M01AB05
• Ibuprofen	M01AE01
• Indometacin	M01AB01
• Ketoprofen	M01AE03
• Mefanamic acid	M01AG01
• Naproxen	M01AE02
• Piroxicam	M01AC01
COX-2 selective	
• Celecoxib	M01AH01
• Meloxicam	M01AC06
Benzodiazepines	N05BA, N05CD
• Diazepam	N05BA01
• Oxazepam	N05BA04
• Bromazepam	N05BA08
• Aalprazolam	N05BA12
• Nitrazepam	N05CD02
• Flunitrazepam	N05CD03
• Temazepam	N05CD07
• Midazolam	N05CD08

Appendix 1. continued on next page

Medicine Name	**Anatomical Therapeutic Classification codes**
Opioids	NO2A, R05DA04
Weaker opioids	
• Codeine	R05DA04
• Combination codeine preparations	N02AA59, N02AJ06
• Tramadol	N02AX02
• Tapentadol	N02AX06
Stronger opioids	
• Morphine	N02AA01
• Hydromorphone	N02AA03
• Oxycodone	N02AA05
• Oxycodone/naloxone	N02AA55
• Fentanyl	N02AB03
• Methadone	N02AC52
• Buprenorphine	N02AE01

NSAIDs, non-steroidal anti-inflammatory drugs.

Appendix 2. Sensitivity analysis excluding people who reinitiate opioids. Predictors of time to first dose escalation to ≥50 mg oral morphine equivalents (OMEs) per day (cohort 1); time to first dose escalation to ≥90 mg OMEs per day (cohort 2), or time to first transition to strong opioids (cohort 3).

	Cohort 1 initiated on <50mg OMEs/day[1] (n=687,058)	Cohort 2 Initiated on <90mg OMEs/day[1] (n=695,480)	Cohort 3 initiated on weak opioids (n=507,373)
Hazard Ratio (95% Confidence Intervals)			
Demographic characteristics			
Age, years			
18-29	Reference	Reference	Reference
30-44	1.67(1.48-1.89)	1.79(1.53-2.11)	1.12(1.08-1.16)
45-54	2.46(2.18-2.77)	2.70(2.31-3.16)	1.19(1.14-1.24)
55-64	3.17(2.83-3.56)	3.17(2.72-3.70)	1.31(1.26-1.36)
65-74	3.17(2.82-3.57)	3.11(2.65-3.64)	1.58(1.51-1.65)
≥75	3.24(2.87-3.66)	2.78(2.36-3.26)	1.96(1.87-2.05)
Sex, female	0.81(0.78-0.85)	0.72(0.69-0.76)	0.94(0.92-0.96)
Concessional beneficiary	1.24(1.17-1.31)	1.25(1.16-1.34)	0.89(0.87-0.91)
Comorbidities*			
Total number**	1.02(1.01-1.03)	1.02(1.00-1.03) p=0.0125	1.03(1.03-1.04)
Cancer treatment history	3.10(2.89-3.33)	3.91(3.60-4.25)	2.04(1.92-2.17)
Depression	1.20(1.14-1.25)	1.18(1.11-1.25)	1.18(1.15-1.21)
Prior use of selected medication in the past 3 months			
Benzodiazepines	1.21(1.14-1.29)	1.22(1.14-1.31)	1.20(1.16-1.24)
Paracetamol	1.15(1.09-1.21)	1.08(1.01-1.16) p=0.0347	1.07(1.03-1.11) p=0.0002
Pregabalin	1.56(1.44-1.69)	1.54(1.40-1.69)	1.37(1.31-1.44)
NSAIDs	1.16(1.10-1.21)	1.05(0.99-1.12) p=0.1039	1.25(1.22-1.28)
Prescriber, general practitioner	1.11(1.06-1.16)	1.04(0.99-1.10) p=0.1463	0.94(0.92-0.96)

Cox proportional hazard models were used to estimate the hazard ratios. The model was adjusted for all variables in the table. All p values were <0.0001, except where specified.

[1] Calculated as an average dose per day in the first month of opioid initiation

*Determined by RxRisk-V at baseline and in the 12-months prior to opioid initiation. RxRisk-V uses records of dispensed medications to identify probable medical conditions.

** Total number excludes cancer treatment history, opioid and NSAID treated pain, anxiety and depression treatment history.

Chapter Six - Trajectories of sickness absence and disability pension before and after opioid initiation for non-cancer pain: 10-year population-based study

Chapters Two to Five investigated patterns of opioid use that have been associated with harm in the US and Canada. These Chapters have shown that similar trends and patterns of opioid use are being prescribed and dispensed in Australia. Australia is also experiencing similar trends in opioid-related harm and is at risk of facing the scale of harm reported in the US and Canada. The increase in prescription opioid analgesic use and harm has been mainly attributed to increased prescribing of opioids for CNCP.

It is well known that CNCP is leading cause of disability. The focus of CNCP management has started to shift to improving function rather than treating pain scores in isolation. Impaired function due to pain is responsible for many detrimental effects including interfering with daily activities, physical and mental health, family and social relationships, and interactions in the workplace. Our review of the literature found mixed results on the management of CNCP with opioids and their effects on capacity and ability to work. Indirect cost related to work disability has been identified as the largest contributor to the cost associated with CNCP.

At the time of this thesis, it was not possible to investigate opioid use and work disability in the whole Australian population. However, because an individual's capacity to work was identified as an important outcome for individuals with CNCP, a collaboration with Sweden was established. Consequently, I went to Sweden to analyse their linked nationwide register data. The same methodology applied in Chapter Four was used in this study. Group based trajectory modelling provided the opportunity to model sickness absence and disability pension days/year over a 10-year period. People initiating opioids in 2009 were identified and their patterns of sickness absence and disability pension were modelled 5 years before and after opioid initiation for non-cancer pain. Due to the richness in data available through the Swedish linked registers, a range

of important sociodemographic and medication-related factors could be investigated, including those identified in Chapters Two to Five.

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Research Paper

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Trajectories of sickness absence and disability pension before and after opioid initiation for noncancer pain: a 10-year population-based study

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Abstract

Chronic noncancer pain is a leading cause of sickness absence (SA) and disability pension (DP). The objectives of this study were to identify trajectories of SA/DP before and after strong and weak opioid initiation for noncancer pain and the factors associated with these trajectories. A longitudinal population-based study of 201,641 people (24-59 years) without cancer who initiated opioid analgesics in 2009 in Sweden was conducted. Trajectories of net annual SA/DP days in the 5 years before/after opioid initiation were estimated with group-based trajectory modelling. Multinomial logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with trajectory groups. Among the 6.9% of people initiating strong opioids, 12.5% had persistent high SA/DP (estimated 320 days/year) before and after opioid initiation and 72.9% had persistent low/minimum SA/DP (estimated 30 days/year). Approximately 8.6% of people had increasing SA/DP, and 6.1% had decreasing SA/DP after opioid initiation, although this seemed to reflect continuation of preinitiation patterns. Trajectories were similar at lower SA/DP days/year among those initiating weak opioids. Persistent high SA/DP among strong opioid initiators were associated with ≥5 comorbidities (OR = 8.72, 95% CI 5.61-13.56), ≤9 years of education (OR = 5.83, 95% CI 4.84-7.03), and previous use of antidepressants (OR = 4.57, 95% CI 3.89-5.37) and antipsychotics (OR = 4.49, 95% CI 2.93-6.88). Three-quarters of people initiating opioids for noncancer pain had persistent low/minimum levels of SA/DP 5 years before and after initiation. Increasing and decreasing SA/DP after opioid initiation seemed to reflect a continuation of preinitiation patterns. Our findings highlight the complex range of sociodemographic and medication-related factors associated with persistent SA/DP.

Keywords: Opioid analgesics, Chronic noncancer pain, Sick leave, Disability pension, Trajectory analysis, Sweden

1. Introduction

Optimizing pain management is important because pain interferes with daily activities, physical and mental health, family and social relationships, and interactions in the workplace.[15] Chronic noncancer pain (CNCP) is a leading cause of disability worldwide[18] and often affects an individual's short- and long-term capacity to work.[20] Work incapacity due to CNCP can be temporary, leading to sickness absence (SA), or permanent, resulting in long-term disability and receipt of disability pension (DP). Absenteeism due to CNCP is a major cause of lost productivity worldwide.[17,31,37] In Sweden, indirect costs associated with lost productivity due to SA from chronic pain was estimated to be SEK 80 billion (€7.7 billion) in 2003.[31] Chronic noncancer pain may limit a person's ability to obtain or maintain employment,[7,38] and therefore, optimizing pain management benefits the individual, their family, and society.

Over the past decade, worldwide opioid analgesic use more than doubled from 3.01 billion statistical defined daily doses in 2001-2003 to 7.35 billion statistical defined daily doses in 2011-2013.[6] This steep increase in opioid use is mainly attributable to the prescribing of opioids (particularly strong opioids[24,25]) for CNCP.[8] Opioid prescribing for CNCP remains controversial because of limited evidence for long-term effectiveness and potential for adverse events.[9] However, guidelines recommend patients may trial opioids if the expected improvements in pain and function are anticipated to outweigh the risk of adverse events.[13,14,22] Hence, pain is often managed with opioids before, during, or after SA or going onto DP with the aim of improving pain and overall functioning.

Research in the United States found that higher opioid doses of >60 oral morphine equivalent (OME) milligrams per day were associated with lower rates of return to work and work retention, as well as higher health care utilization among workers with chronic musculoskeletal conditions.[27] In an overview of systematic reviews, Deyo et al.[10] concluded that there is no evidence

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that prescribing opioids for back pain improves return-to-work rates. In addition, a retrospective cohort study of US veterans admitted to a CNCP rehabilitation program found that opioid cessation among those with high levels of impairment may occur without negatively impacting treatment effectiveness.[32] The same study also found that some domains of function, including activities of daily living, may be enhanced after opioid cessation.[32] This may be because opioids can cause tolerance, hyperalgesia,[42] and sedation that affect pain control, concentration, functional status, and work productivity.[11] However, it is unclear how initiation of strong and weak opioid analgesics is associated with long-term patterns of SA/DP. Previous studies have highlighted the importance of sociodemographic factors, such as age, sex, country of birth, education level, family situation, and living area as potential determinants of SA/DP.[1,2,20] Therefore, the objectives of this study were to identify trajectories of SA/DP before and after strong and weak opioid initiation, respectively, for noncancer pain and the sociodemographic and medication-related factors associated with such trajectories.

2. Method

2.1. Study design, setting, and data sources

A longitudinal population-based retrospective study of all working-age residents in Sweden was undertaken to investigate SA/DP 5 years before and after opioid initiation in 2009. Opioid initiators were identified through the Swedish Prescribed Drug Register, maintained by the National Board of Health and Welfare. Sociodemographic variables were obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) maintained by Statistics Sweden. Data regarding SA and DP were obtained from the Micro Data for Analysis of the Social Insurance register maintained by the National Social Insurance Agency. Details on cancer diagnosis were obtained from the Swedish Cancer Register, and date of death was extracted from the Cause of Death Register. Both registers are maintained by the National Board of Health and Welfare. Register linkage was performed using each individual's personal identification number. This is a unique 10-digit number assigned to all residents in Sweden.

2.2. Study population and definition of opioid use

The study sample included adults aged 18 to 64 years in 2004-2014. To allow for the cohort to be of working age in all 10 years studied, all persons aged 24 to 59 years who initiated opioid analgesics in 2009 were included. The date of the first dispensing of an opioid in 2009 was denoted as the "index" date (Y_0). New opioid initiators were defined as those with no opioid dispensings in the previous 12 months. In Sweden, opioids are only available through prescription, and all opioid dispensings are included in the Swedish Prescribed Drug Register. Data on dispensed medications of interest were identified in the drug register and categorized using the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system (Appendix A, available at http://links.lww.com/PAIN/A744).[9] The ATC classification system is an international method for comparing active ingredients of medications based on the organ systems on which they act. Individual opioids were further categorized as weak or strong according to their potency.[14] Appendix A shows this categorization using the drug name and the respective ATC code (available at http://links.lww.com/PAIN/A744). People dispensed both strong and weak opioids at the date of initiation were categorized as strong opioid initiators. Initial opioid characteristics including type of opioid dispensed and total OME in mg were also determined. Oral morphine equivalent is a relative measure used clinically to determine dose equivalence to oral morphine.[35] To determine OME, a conversion factor specific to an opioid and its route of administration is used. Total OMEs dispensed were calculated using the following formula: (pack strength * OME conversion factor of opioid dispensed[35] * quantity dispensed). This can be used as a surrogate for dose and duration of an opioid dispensing in prescription registry data. For example, 45 tablets of 10 mg oral morphine (OME = 450 mg) and 20 capsules of 10 mg oxycodone (OME = 300 mg) dispensed to an individual at the "index" date would total 750 mg OME. In Sweden, the maximum amount of medication prescribed for each dispensing (including opioids) is typically 3 months.[44] People who initiated opioids in combination with antispasmodics (ATC N02AG), topical opioids (ie, gels and creams), and extemporaneously prepared opioids were excluded because we did not have sufficient information to calculate OME. As the focus of this study was on opioid use for noncancer pain, people with a cancer diagnosis recorded in the cancer register at baseline or in the 12 months before the initial opioid dispensing were excluded (n = 3874).

2.3. Sickness absence and disability pension

Sweden has a nationwide public insurance system for SA and DP. All individuals receiving income from work or unemployment benefits can, from the age of 16 years, receive SA benefits if their work capacity is reduced due to disease or injury.[43] Disability pension can be granted to all residents aged 19 to 64 years if a disease or injury leads to long-term or permanent work incapacity. The first 14 days of SA are usually paid by the employer and therefore not included in the Micro Data for Analysis of the Social Insurance register. Sickness absence/DP can be received for full-time or part-time (25, 50, or 75%) of ordinary working hours. This means that people can receive both part-time SA and DP concurrently. In this study, we included all SA episodes that were >14 days and extrapolated the full-time or part-time status of the first 14 days based on the SA status on day 15. Sickness absence/DP was defined as the combined annual number of compensated net absence days from work due to SA and DP for each person. The net annual days of SA/DP for 5 years before (Y − 5) and 5 years after (Y + 5) the date of opioid initiation were calculated (eg, 2 absence days of 50% were combined to 1 net day). Individuals who immigrated (n = 7363), emigrated (n = 1424), or died (n = 3469) during the 10-year period were considered as having 0 net days of SA/DP for the corresponding year(s) where they were not at risk of SA/DP. In total, 11,461 people emigrated, immigrated, and/or died during the study period.

2.4. Sociodemographic and previous medication use characteristics

Sociodemographic variables including age, level of education, country of birth, type of living area, and family situation were assessed in 2009 to correspond to the year of opioid initiation. The highest level of education attained by each person was categorized as: compulsory (≤9 years of education), high school (10-12 years of education), and university education (>12 years of education). Type of living area was based on population density according to the H-region classification scheme: larger cities (H1-H2: Stockholm [>900,000 inhabitants], Gothenburg [>500,000

inhabitants], and Malmö [>300,000 inhabitants]); medium-sized cities (H3-H4: cities with >90,000 inhabitants within 30 km distance from the centre of the city); small cities/villages/rural (H5-H6).[4] A look-back period of 12 months was used to identify incident opioid use and to determine the total number of comorbidities and previous medication use. The number of comorbidities was estimated using the 45-item RxRisk tool.[29] This is a validated medication-based comorbidity index developed for use with administrative claims data. Anxiety, depression, pain, and psychotic disorders were excluded from the total number of comorbidities because these were analyzed separately. As individuals on SA due to mental disorders have a higher number of SA episodes and duration of SA,[36] previous use of psychotropic medications (benzodiazepines, antidepressants, and antipsychotics) was also determined (Appendix A, available at http://links.lww.com/PAIN/A744). Previous use of nonopioid analgesics, including paracetamol and nonsteroidal anti-inflammatory medications, was examined to determine previous pain treatment (Appendix A, available at http://links.lww.com/PAIN/A744).

2.5. Statistical analyses

The sociodemographic and previous medication use characteristics are presented as frequencies and percentages or mean and SD. Trajectories of net annual SA/DP days for people who were initiated on strong opioids (model 1) or weak opioids (model 2) were estimated during a 10-year period (5 years before and after opioid initiation) with group-based trajectory modelling (GBTM).[33,34] Group-based trajectory modelling is a method designed to identify clusters of individuals (trajectory groups), who have followed a similar trajectory of an outcome (SA/DP) over time.[34] This is useful because the pattern of SA/DP for individuals is not necessarily consistent over the follow-up (eg, some people have all SA/DP days at the start of the follow-up, and other people have the same number of SA/DP days spread across the entire follow-up period). The trajectory groups are defined by the data and used as a statistical device in GBTM for approximating the unknown distribution of trajectories across population members.[34] In our study, patterns of SA/DP days over time of the population were used to assign people to various trajectories based on the highest estimated probability that they belong in that group. A fifth-order (or quintic polynomial) trajectory model with 5 groups was determined to have the best overall model fit based on the highest Bayesian information criterion, the posterior probabilities and group membership of ≥5% for those initiating strong opioids.[3,34] Similarly, a fifth-order trajectory model with 4 groups was determined to have the best overall model fit for those initiating weak opioids.[3,34] Among strong opioid initiators, the average posterior probability (SD) for each of the 5 trajectory groups ranged from 0.92 (0.11) to 0.99 (0.06). The average posterior probability (SD) for each of the 4 trajectory groups for weak opioid initiators ranged from 0.90 (0.15) to 0.99 (0.06). This indicates good internal reliability on the basis of the 0.7 threshold recommended by Nagin and Odgers.[34] Multinomial logistic regression models were used to analyze the association between sociodemographic and medication-related characteristics and SA/DP trajectories. Separate models were conducted for strong and weak opioid initiators. Multicollinearity between variables was assessed using tolerance, variance inflation factors, eigenvalues, and the condition index. There was no evidence of multicollinearity between variables in any of the models. Adjusted odds ratios (OR) and 95% confidence intervals (CI) are reported. To investigate the possible impact of death, immigration, or emigration during the study period, sensitivity analyses were conducted excluding people who fulfilled these criteria. SAS version 9.4 (SAS, Cary, NC) was used for all analyses.

2.6. Ethical approval

The project was approved by the Regional Ethical Review Board of Stockholm, Sweden. The study was also approved by the Monash University Human Research Ethics Committee.

3. Results

3.1. Cohort

There were 201,641 people aged 24 to 59 years who initiated opioid analgesics in 2009. Of these, 54% were women, and the mean age was 43.2 (SD 10.0) years (**Table 1**). The majority of the cohort were born in Sweden (78.4%) and lived in larger cities (44.1%). Half of the cohort (50.3%) had a high school education as their highest level of education. Overall, weak opioids including codeine combinations (43.2%), followed by tramadol (35.8%) and dextropropoxyphene (14.9%), were the most commonly initiated opioids among the cohort (Appendix B, available at http://links.lww.com/PAIN/A744).

In the cohort, 13,976 (6.9%) people initiated strong opioids. The mean number of comorbidities (SD) for strong opioid initiators was 1.4 ± 0.8 and 1.2 ± 0.7 for weak opioid initiators. Previous nonopioid analgesic use was more common among the strong opioid initiators than among the weak opioid initiators (84.2% vs 63.1%) (Appendix C, available at http://links.lww.com/PAIN/A744). This difference was mainly attributed to higher paracetamol use among strong vs weak opioid initiators (73.7% vs 37.7%).

3.2. Sickness absence/disability pension trajectories among strong opioid initiators

Five groups of SA/DP trajectories (named: minimal, persistent low, increasing, decreasing, and persistent high) were identified among strong opioid initiators (**Fig. 1**). Most people belonged to the "minimal SA/DP" group (41.8%), followed by the "low SA/DP" group (31.1%). Although these groups are similar, the "minimal SA/DP" group includes an increase in SA/DP days/year from 2 years before opioid initiation, with a peak at 1 year after opioid initiation, followed by a decrease to zero SA/DP days/year 2 years after opioid initiation. In comparison, the "persistent low" trajectory group has a smooth shape. Sickness absence/DP increased from 70 days/year in 2004 to 200 days/year in 2011 in the "increasing SA/DP" group. In the "decreasing SA/DP" group, SA/DP decreased from 200 days/year in 2004 to 30 days/year in 2012.

3.3. Sickness absence/disability pension trajectories among weak opioid initiators

Four groups (minimal, increasing, decreasing, and persistent high) were identified among weak opioid initiators (**Fig. 2**). Most people (74.1%) belonged to the "minimal SA/DP" group. Among weak opioid initiators belonging to the "increasing SA/DP" group, SA/DP increased from 50 days/year in 2008 to 150 days/year in 2014. In the "decreasing SA/DP" group, SA/DP decreased from 200 days/year in 2006 to 80 days/year in 2014.

3.4. Comparison of sickness absence/disability pension trajectories among strong and weak opioid initiators

Strong opioid initiators had a higher proportion of individuals in the "persistent high SA/DP" group than the weak opioid initiators

Table 1

Sociodemographic characteristics, previous comorbidities, sickness absence (SA), and disability pension (DP) among all people who initiated opioid analgesics in 2009.

	All (n = 201,641)	Weak opioid initiators (n = 187,665)	Strong opioid initiators (n = 13,976)
N (%) or mean ±SD			
Age, years*	43.2 ± 10.0	43.0 ± 10.0	45.6 ± 9.7
24-29	23,412 (11.6)	22,309 (11.9)	1103 (7.9)
30-39	51,387 (25.5)	48,680 (25.9)	2707 (19.4)
40-49	62,645 (31.1)	58,232 (31.0)	4413 (31.6)
50-59	64,197 (31.8)	58,444 (31.1)	5753 (41.2)
Sex, women	108,889 (54.0)	102,019 (54.4)	6870 (49.2)
Education (years)			
University (>12)	63,698 (31.6)	59,347 (31.6)	4351 (31.1)
High school (10-12)	101,399 (50.3)	94,293 (50.3)	7106 (50.8)
Compulsory (≤9)	36,544 (18.1)	34,025 (18.1)	2519 (18.0)
Country of birth			
Sweden	158,069 (78.4)	146,551 (78.1)	11,518 (82.4)
Other European countries	12,154 (6.0)	11,287 (6.0)	867 (6.2)
Rest of the world	31,418 (15.6)	29,827 (15.9)	1591 (11.4)
Type of living area†			
Larger cities	88,837 (44.1)	83,440 (44.5)	5397 (38.6)
Medium-sized cities	63,377 (31.4)	58,684 (31.3)	4693 (33.6)
Small towns/villages	49,427 (24.5)	45,541 (24.3)	3886 (27.8)
Family situation			
Married/cohabiting			
No children at home	24,582 (12.2)	22,532 (12.0)	2050 (14.7)
Children at home	87,643 (43.5)	82,136 (43.8)	5507 (39.4)
Single			
No children at home	67,413 (33.4)	62,412 (33.3)	5001 (35.8)
Children at home	22,003 (10.9)	20,585 (11.0)	1418 (10.2)
Comorbidities‡			
Total number§	1.2 ± 0.7	1.2 ± 0.7	1.4 ± 0.8
0	23,486 (11.7)	22,936 (12.2)	550 (3.9)
1-2	126,310 (62.6)	117,917 (62.8)	8393 (60.1)
3-4	37,122 (18.4)	33,791 (18.0)	3331 (23.8)
≥5	14,723 (7.3)	13,021 (6.9)	1702 (12.2)
Previous SA/DP (net days)‖			
0	123,140 (61.1)	118,692 (63.3)	4448 (31.8)
1-180	47,948 (23.8)	41,530 (22.1)	6418 (45.9)
≥181	30,553 (15.2)	27,443 (14.6)	3110 (22.3)
Died during follow-up	3469 (1.7)	2866 (1.5)	603 (4.3)

* Measured in 2009.

† Type of living area was based on population density according to the H-region classification scheme: larger cities (H1-H2: Stockholm, Gothenburg, and Malmö); medium-sized cities (H3-H4: cities with more than 90,000 inhabitants within 30 km distance from the centre of the city); and small cities/villages/rural (H5-H6)[4]

‡ Determined using the 45-item RxRisk tool and measured for the 365 days before and including the date of opioid initiation.

§ Excludes anxiety, depression, pain, and psychotic disorders as these are investigated separately as medication classes.

‖ Net days of SA/DP in the 365 days before and including the date of opioid initiation.

(12.5% vs 9.1%), with an estimated 320 SA/DP days/year over the study period. There were slightly more individuals in the "increasing SA/DP" groups for both strong and weak opioid initiators than in the "decreasing SA/DP" group (strong: 8.6% vs 6.1%; weak: 8.7% vs 8.0%). Among the strong opioid initiators, the "minimal SA/DP" group had increased SA/DP days/year during Y − 1, which increased from approximately 30 days/year to 50 days/year and then decreased to no/minimal levels of SA/DP. This was not seen among weak opioid initiators.

3.5. Factors associated with sickness absence/disability pension trajectories among strong opioid initiators

Among strong opioid initiators, the strongest adjusted associations compared with the "minimal SA/DP" trajectory are outlined below (**Table 2**). Previous antidepressant use (OR = 3.99, 95% CI 3.36-4.74) and having ≥5 comorbidities (OR = 4.92, 95% CI 3.13-7.72) were associated with the "increasing SA/DP" trajectory. Having a compulsory education (OR = 3.46, 95% CI 2.75-4.37), having ≥5 comorbidities (OR = 4.52, 95% CI 2.81-7.26), and previous antidepressant use (OR = 3.85, 95% CI 3.18-4.67) were associated with the trajectory named "decreasing SA/DP." Having a compulsory education (OR = 5.83, 95% CI 4.84-7.03) and having ≥5 comorbidities (OR = 8.72, 95% CI 5.61-13.56) were also strongly associated with the "persistent high SA/DP" trajectory.

3.6. Factors associated with sickness absence/disability pension trajectories among weak opioid initiators

Among weak opioid initiators, the strongest adjusted associations compared with the "minimal SA/DP" trajectory are outlined

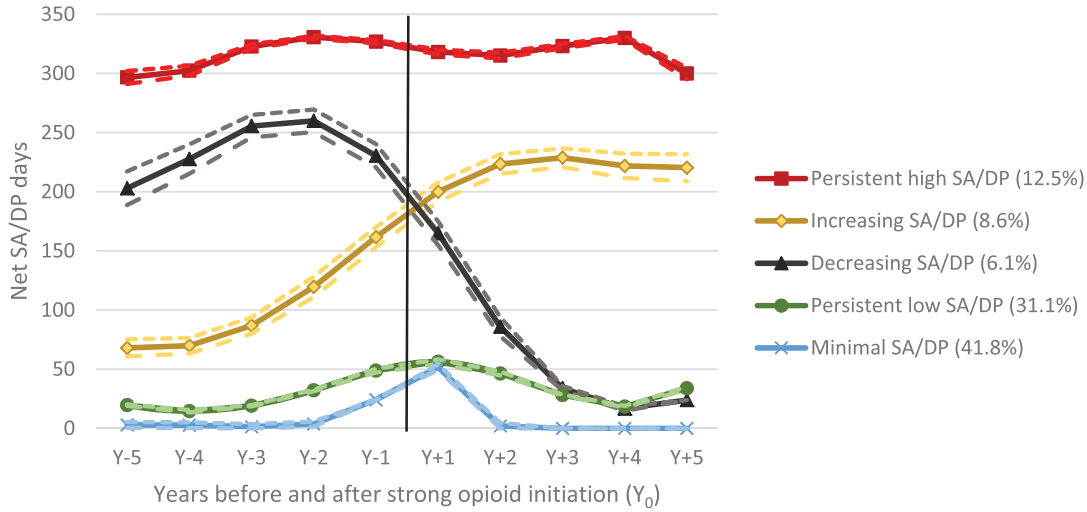

Figure 1. The 5 identified trajectories of net annual sickness absence (SA) and disability pension (DP) days among strong opioid initiators (n = 13,976) 5 years before and 5 years after opioid initiation. Date of opioid initiation (Y_0) is between Y − 1 and Y + 1 and is represented by the vertical line. For each trajectory, the solid lines represent the predicted trajectory, and the broken lines represent the 95% confidence intervals. The legend indicates the percentage of the cohort belonging to each trajectory.

below (**Table 3**). Having ≥5 comorbidities (OR = 3.72, 95% CI 3.00-3.56) was associated with the "increasing SA/DP" trajectory. Previous antidepressant (OR = 3.73, 95% CI 3.57-3.89) and antipsychotic (OR = 3.39, 95% CI 2.98-3.86) use and having ≥5 comorbidities (OR = 3.84, 95% CI 3.50-4.22) were associated with the "decreasing SA/DP" trajectory. Having a compulsory education (OR = 6.12, 95% CI 5.78-6.49) and having ≥5 comorbidities (OR = 5.85, 95% CI 5.30-6.45) were associated with the "persistent high SA/DP" trajectory.

3.7. Sensitivity analyses

Excluding people who immigrated, emigrated, and/or died did not change the trajectory patterns among strong opioid initiators (Appendix D, available at http://links.lww.com/PAIN/A744). However, the proportion of weak opioid initiators belonging to the "decreasing SA/DP" group was slightly lower in the sensitivity analysis compared with the main analysis (main analysis: 8.7%; sensitivity analysis: 8.0%). The strength and significance of associations were very similar in all the sensitivity analyses compared with the main analyses in both groups.

4. Discussion

This is the first longitudinal population-based study to investigate SA/DP trajectories before and after opioid initiation among people with noncancer pain. The main findings of this study were that three-quarters of people initiating opioids had persistent low/minimal levels of SA/DP (estimated 30 days/year) in the 5 years before and after opioid initiation. Of those initiating strong opioids, SA/DP days/year increased in 8.6% of people and decreased in 6.1% of people. Increasing and decreasing patterns of SA/DP

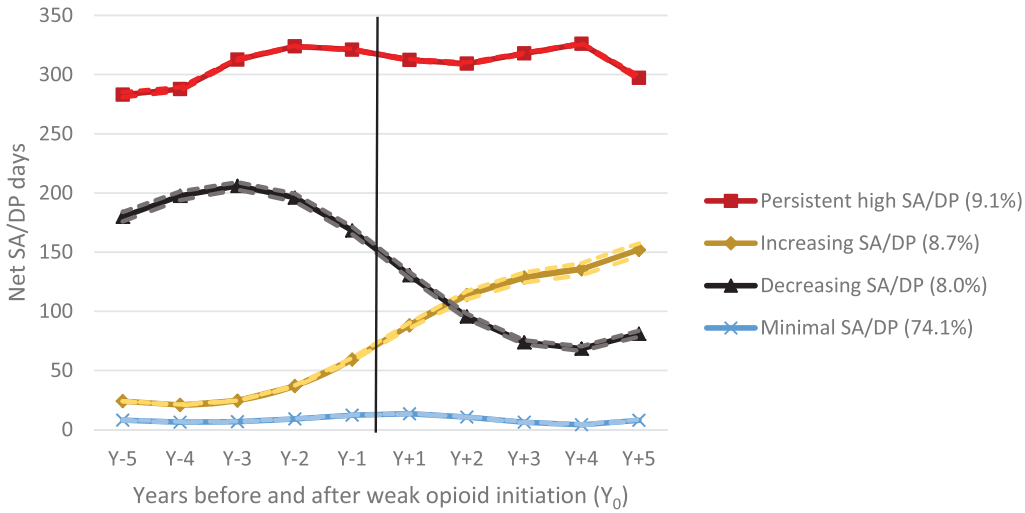

Figure 2. The 4 identified trajectories of net annual sickness absence (SA) and disability pension (DP) days among weak opioid initiators (n = 187,665) 5 years before and 5 years after opioid initiation. Date of opioid initiation (Y_0) is between Y − 1 and Y + 1 and is represented by the vertical line. For each trajectory, the solid lines represent the predicted trajectory, and the broken lines represent the 95% confidence intervals. The legend indicates the percentage of the cohort belonging to each trajectory.

Table 2

Factors associated with each sickness absence (SA)/disability pension (DP) trajectory among strong opioid initiators using "minimal SA/DP" trajectory group as the reference (n = 5839).

	Persistent low SA/DP (n = 4346)	Increasing SA/DP (n = 1199)	Decreasing SA/DP (n = 847)	Persistent high SA/DP (n = 1745)
Adjusted odds ratio (95% confidence interval)				
Age, y*				
24-29	**0.80 (0.68-0.94)**	**0.67 (0.48-0.93)**	**0.49 (0.33-0.73)**	**0.27 (0.18-0.41)**
30-39	Reference	Reference	Reference	Reference
40-49	1.00 (0.90-1.12)	**1.46 (1.19-1.79)**	**1.42 (1.13-1.78)**	**2.12 (1.72-2.60)**
50-59	1.11 (0.99-1.24)	**1.89 (1.55-2.32)**	**1.51 (1.20-1.89)**	**3.11 (2.54-3.81)**
Sex, women	**1.83 (1.70-1.99)**	**2.33 (2.03-2.68)**	**2.54 (2.16-2.98)**	**2.86 (2.51-3.26)**
Education (y)*				
University (>12)	Reference	Reference	Reference	Reference
High school (10-12)	**1.59 (1.45-1.74)**	**2.40 (2.04-2.81)**	**2.88 (2.38-3.49)**	**3.52 (2.99-4.14)**
Compulsory (≤9)	**1.38 (1.21-1.56)**	**2.51 (2.06-3.07)**	**3.46 (2.75-4.37)**	**5.83 (4.84-7.03)**
Country of birth				
Sweden	Reference	Reference	Reference	Reference
Other European countries	0.86 (0.73-1.03)	0.85 (0.64-1.13)	0.84 (0.61-1.16)	1.04 (0.82-1.32)
Rest of the world	**0.85 (0.74-0.98)**	**1.57 (1.28-1.92)**	1.25 (0.98-1.59)	**1.89 (1.56-2.27)**
Type of living area†				
Larger cities	Reference	Reference	Reference	Reference
Medium-sized cities	1.09 (0.99-1.20)	**1.43 (1.22-1.68)**	**1.40 (1.17-1.68)**	**1.71 (1.47-1.99)**
Small towns/villages	**1.18 (1.07-1.31)**	**1.74 (1.47-2.05)**	**1.50 (1.24-1.81)**	**1.96 (1.68-2.30)**
Family situation				
Married/cohabiting				
No children at home	Reference	Reference	Reference	Reference
Children at home	**0.87 (0.76-0.99)**	**0.71 (0.58-0.87)**	1.01 (0.79-1.30)	**0.71 (0.59-0.86)**
Single				
No children at home	0.92 (0.80-1.06)	0.95 (0.78-1.16)	**1.48 (1.16-1.90)**	**1.61 (1.34-1.93)**
Children at home	1.05 (0.88-1.25)	1.05 (0.81-1.36)	**1.42 (1.05-1.93)**	1.07 (0.83-1.37)
Comorbidities‡				
0	Reference	Reference	Reference	Reference
1-2	**1.32 (1.06-1.64)**	1.33 (0.87-2.02)	0.99 (0.64-1.55)	**1.54 (1.01-2.34)**
3-4	**2.09 (1.65-2.63)**	**2.77 (1.80-4.28)**	**2.44 (1.55-3.85)**	**3.95 (2.57-6.06)**
≥5	**2.35 (1.81-3.04)**	**4.92 (3.13-7.72)**	**4.52 (2.81-7.26)**	**8.72 (5.61-13.56)**
OME in mg dispensed				
Total OME <250	Reference	Reference	Reference	Reference
Total OME 250-499	1.02 (0.92-1.14)	**1.33 (1.12-1.57)**	**1.50 (1.23-1.82)**	**1.37 (1.17-1.59)**
Total OME 500-749	**1.15 (1.03-1.30)**	**1.29 (1.06-1.57)**	**1.55 (1.24-1.94)**	1.01 (0.83-1.22)
Total OME 750-1000	**1.20 (1.03-1.41)**	**1.53 (1.19-1.97)**	**1.79 (1.35-2.39)**	**1.39 (1.10-1.76)**
Total OME >1000	**1.33 (1.15-1.54)**	**2.21 (1.79-2.74)**	**1.98 (1.53-2.56)**	**1.51 (1.22-1.86)**
Prior use of medication of interest (yes/no)				
Benzodiazepines	1.20 (1.00-1.44)	**1.91 (1.52-2.40)**	**2.19 (1.71-2.81)**	**3.20 (2.62-3.90)**
Antidepressants	**1.79 (1.56-2.05)**	**3.99 (3.36-4.74)**	**3.85 (3.18-4.67)**	**4.57 (3.89-5.37)**
Antipsychotics	0.73 (0.44-1.22)	**2.34 (1.42-3.83)**	**2.30 (1.36-3.89)**	**4.49 (2.93-6.88)**
Paracetamol	**0.86 (0.77-0.95)**	**0.75 (0.64-0.88)**	**0.68 (0.57-0.81)**	**0.63 (0.54-0.73)**
NSAIDs	**1.23 (1.14-1.34)**	**1.29 (1.13-1.48)**	**1.21 (1.04-1.41)**	**1.02 (0.90-1.15)**

Bold values indicate statistical significance at $P < 0.05$. Adjusted for all the other variables listed in Table 2.

* Measured in 2009.

† Type of living area was based on population density according to the H-region classification scheme: larger cities (H1-H2: Stockholm, Gothenburg, and Malmö); medium-sized cities (H3-H4: cities with more than 90,000 inhabitants within 30-km distance from the centre of the city); and small cities/villages/rural (H5-H6)[24]

‡ Determined using the 45-item RxRisk tool and measured for the year before and including date of opioid initiation. Total number of comorbidities excludes anxiety, depression, pain, and psychotic disorders, as these are investigated separately as medication classes.

NSAID, nonsteroidal anti-inflammatory medication; OME, oral morphine equivalent.

after opioid initiation seemed to reflect a continuation of the preinitiation patterns. In total, 12.5% of strong opioid initiators and 9.5% of weak opioid initiators had persistent high SA/DP days/year (estimated 320 SA/DP days/year). Importantly, we identified a range of sociodemographic and medication-related factors associated with this high SA/DP trajectory, including higher age, more comorbidities, socioeconomic disadvantage, previous medication use for mental conditions, and higher initial OMEs. These associations with SA/DP have not been reported previously among people initiating opioids.

Most people initiating strong or weak opioids had persistent low/minimal SA/DP days/year over the 10-year period. These levels of SA/DP days/year were broadly consistent with those observed in the Swedish general population over the same

Table 3

Factors associated with each sickness absence (SA)/disability pension (DP) trajectory among weak opioid initiators using "minimal SA/DP group" as the reference (n = 139,123).

	Increasing SA/DP (n = 16,358)	Decreasing SA/DP (n = 15,044)	Persistent high work SA/DP (n = 17,140)
Adjusted odds ratio (95% confidence interval)			
Age, y*			
24-29	**0.79 (0.74-0.84)**	**0.45 (0.41-0.49)**	**0.45 (0.41-0.50)**
30-39	Reference	Reference	Reference
40-49	**1.07 (1.02-1.12)**	**1.47 (1.40-1.55)**	**2.40 (2.26-2.55)**
50-59	**1.31 (1.25-1.38)**	**1.90 (1.81-2.00)**	**4.17 (3.93-4.43)**
Sex, women	**1.67 (1.61-1.73)**	**2.20 (2.12-2.29)**	**2.24 (2.16-2.33)**
Education (y)*			
University (>12)	Reference	Reference	Reference
High school (10-12)	**1.81 (1.73-1.88)**	**2.08 (1.99-2.18)**	**3.10 (2.95-3.27)**
Compulsory (≤9)	**2.01 (1.91-2.12)**	**2.56 (2.42-2.70)**	**6.12 (5.78-6.49)**
Country of birth			
Sweden	Reference	Reference	Reference
Other European countries	1.06 (0.99-1.14)	**0.92 (0.85-0.99)**	**1.39 (1.30-1.48)**
Rest of the world	**1.16 (1.10-1.21)**	**0.91 (0.87-0.96)**	**1.56 (1.49-1.64)**
Type of living area†			
Larger cities	Reference	Reference	Reference
Medium-sized cities	**1.28 (1.23-1.33)**	**1.31 (1.26-1.37)**	**1.41 (1.35-1.47)**
Small towns/villages	**1.31 (1.26-1.37)**	**1.40 (1.34-1.46)**	**1.54 (1.47-1.61)**
Family situation			
Married/cohabiting			
No children at home	Reference	Reference	Reference
Children at home	0.97 (0.92-1.03)	0.98 (0.93-1.04)	**0.76 (0.72-0.81)**
Single			
No children at home	**1.18 (1.12-1.25)**	**1.29 (1.21-1.37)**	**1.73 (1.64-1.83)**
Children at home	**1.20 (1.12-1.28)**	**1.24 (1.16-1.33)**	**1.10 (1.03-1.19)**
Comorbidities‡			
0	Reference	Reference	Reference
1-2	**1.37 (1.28-1.46)**	**1.43 (1.32-1.55)**	**1.43 (1.31-1.57)**
3-4	**2.19 (2.04-2.36)**	**2.37 (2.18-2.57)**	**2.83 (2.58-3.10)**
≥5	**3.27 (3.00-3.56)**	**3.84 (3.50-4.22)**	**5.85 (5.30-6.45)**
OME in mg dispensed			
Total OME <250	Reference	Reference	Reference
Total OME 250-499	**1.19 (1.14-1.24)**	**1.19 (1.13-1.24)**	**1.26 (1.20-1.32)**
Total OME 500-749	**1.28 (1.21-1.35)**	**1.23 (1.16-1.31)**	**1.27 (1.19-1.35)**
Total OME 750-1000	**1.41 (1.33-1.54)**	**1.62 (1.54-1.71)**	**1.67 (1.58-1.77)**
Total OME >1000	**1.82 (1.65-2.01)**	**2.75 (2.51-3.01)**	**3.16 (2.89-3.46)**
Prior medication use (yes/no)			
Antidepressants	**2.52 (2.41-2.63)**	**3.73 (3.57-3.89)**	**3.87 (3.70-4.04)**
Antipsychotics	**2.36 (2.05-2.71)**	**3.39 (2.98-3.86)**	**8.28 (7.42-9.24)**
Benzodiazepines	**1.57 (1.47-1.67)**	**1.58 (1.48-1.69)**	**2.85 (2.69-3.02)**
NSAIDs	**1.29 (1.25-1.33)**	1.01 (0.97-1.04)	**0.86 (0.83-0.89)**
Paracetamol	**1.11 (1.07-1.15)**	**1.31 (1.26-1.36)**	**1.41 (1.35-1.46)**

Bold values indicate statistical significance at $P < 0.05$. Adjusted for all the other variables listed in Table 3.

* Measured in 2009.

† Type of living area was based on population density according to the H-region classification scheme: larger cities (H1-H2: Stockholm, Gothenburg and Malmö); medium-sized cities (H3-H4: cities with more than 90,000 inhabitants within 30-km distance from the centre of the city); and small cities/villages/rural (H5-H6)[24]

‡ Determined using the 45-item RxRisk tool and measured for the year before and including date of opioid initiation. Total number of comorbidities excludes anxiety, depression, pain, and psychotic disorders, as these are investigated separately as medication classes.

NSAID, nonsteroidal anti-inflammatory medication; OME, oral morphine equivalent.

period.[41] It is possible that most of the opioid initiation in these trajectories is for acute rather than CNCP, and this pain may resolve through opioid use, other treatment, or be self-limiting. For example, acute treatment of dental pain, surgical pain, or pain resulting from a fracture. Nevertheless, 12.5% of strong opioid initiators and 9.5% of weak opioid initiators had persistent high SA/DP days/year. These high levels of SA/DP are consistent with those observed among people with CNCP conditions such as rheumatoid arthritis and osteoarthritis.[23] It is likely that opioid use in this trajectory was for CNCP that is complex to manage and requires a multifaceted approach.[26] Our study is important because CNCP is a leading cause of SA/DP. There is minimal evidence to support prescribing opioids for CNCP. Although we cannot exclude the possibility that opioids benefit specific patients, at a population level, opioid initiation did not seem to be associated with a change in pattern of SA/DP. Prospective controlled studies are needed to determine whether opioids promote or prevent return to work among people with leading

causes of disability such as chronic neck and back pain. These are conditions where clinicians are likely to prescribe opioids because other analgesics have been shown to be ineffective or have a small improvement in pain and disability.[16,40]

The majority of working-age people (93.1%) who initiated opioids in Sweden were initiated on weak opioids. This was higher than in an adult Australian population where 72.1% of opioid initiators initiated on weak opioids between 2013 and 2015.[28] Interestingly, in the Tayside region of Scotland, weak opioids were dispensed to 99% of adults dispensed opioids in 1995, compared with 75% of those dispensed opioids in 2010.[39] These variable findings are likely to reflect geographical differences in opioid prescribing preferences and changing patterns of opioid use over time.[22] Duration of SA/DP days/year was slightly lower among weak opioid initiators than among strong opioid initiators. It is likely this was because people with more severe pain were initiated on strong rather than weak opioids. However, there was a higher proportion of people with increasing SA/DP compared with decreasing SA/DP over the 10-year period among both groups. A Finnish study of working-age people investigating SA (≥10 workdays) over a 7-year follow-up period found similar patterns of trajectories in the general population.[21]

Our trajectory models demonstrate association rather than causation between opioid initiation and SA/DP. However, our nationwide data were consistent with several smaller US studies on opioids and work retention. Kidner et al.[27] found that the percentage of people with chronic disabling occupational musculoskeletal disorders reporting work retention ranged from 70.1% in the low opioid subgroup (≤30 OME mg/day) to 55.2% in the very high opioid subgroup (>120 OME mg/day). In addition, a retrospective cohort study of US veterans who had high levels of functional impairment due to CNCP found that people who used opioids could be tapered off opioids without negatively impacting treatment effectiveness, and that some domains of function, including activities of daily living, may be enhanced.[32] It is possible that opioid use may lead to hyperalgesia and tolerance and therefore may be less effective in improving CNCP and function. It is also possible that function could be affected by opioid-related adverse effects (eg, sedation), further prolonging SA/DP.

Previous use of psychotropic medications was strongly associated with higher SA/DP days/year among strong and weak opioid initiators. Previous studies have reported a complex bidirectional relationship between pain and mental disorders.[19] Mental and musculoskeletal disorders are the 2 most common reasons for SA/DP in Sweden.[43] They were also the 2 leading causes of global disease burden, as measured by years lived with disability, in 2010 and 2013.[18] In addition, Dorner et al.[12] reported a higher risk of DP among people with both back pain and common mental disorders (eg, depression and anxiety) than either condition alone.[44] This is consistent with previous use of psychotropic medications being strongly associated with higher levels of SA/DP in our study. This is particularly important because lost work productivity associated with pain and depression has detrimental effects on both individuals and society.[15] Furthermore, indirect costs resulting from lost work productivity contribute to most of the overall societal cost associated with CNCP.[17,31]

4.1. Strengths and limitations

A key strength of our study is the longitudinal design, which involved analyses of SA/DP 5 years before and after opioid initiation for all working-age residents in Sweden. Data linkage permitted consideration of important sociodemographic characteristics and previous medication use not considered in previous studies,[27,30] and sufficient sample size for subgroup analyses. We investigated nationwide trajectories of SA/DP, which identify associations (rather than causation) with opioid initiation. Our data do not directly demonstrate whether strong or weak opioid use promotes or hinders people to return to work. However, we could analyze SA/DP trajectories in relation to the date of opioid initiation rather than based on calendar years. Traditionally, dichotomous outcomes for SA/DP were investigated cross-sectionally; however, by using GBTM, we were able to identify possible trajectories of SA/DP during all the follow-up years. Group-based trajectory modelling was particularly useful because the pattern of SA/DP for individuals is not necessarily consistent over the follow-up. Another strength of this register-based study was that it was not subject to recall error nor to dropout, as information was available for all years included. However, it is possible that some people did not use the medication dispensed. Another advantage of our study is that both net days with SA and DP could be included. Previous studies[5,21] have only assessed SA days, which means that important information on work incapacity is missed. Data were not available on the severity and duration of pain, the indication for opioid use, or information on opioids administrated during inpatient stays at hospitals. Our findings should be interpreted cautiously because prescribed opioid doses and duration of use may vary considerably across countries and between studies. In addition, data were not available on the use of nonpharmacological modalities for the management of pain, which could contribute to improving pain and function and hence, SA/DP patterns. Information on SA episodes shorter than 15 days was not available in our study which means that the number of SA days may have been underestimated; however, it is the longer SA spells that generate most SA days. This means that we included the more severe long-term SA, capturing people with longer work incapacity.

5. Conclusion

More than three-quarters of people who initiate opioids for noncancer pain had persistent low/minimum levels of SA/DP in the 5 years before and after opioid initiation. Increasing and decreasing SA/DP after opioid initiation seemed to reflect a continuation of preinitiation patterns. Higher age, more comorbidities, socioeconomic disadvantage, and previous psychotropic medication use, along with higher initial OMEs, were factors strongly associated with higher SA/DP levels among people initiating weak or strong opioids. Our findings highlight the complex range of sociodemographic and medication-related factors that are associated with persistent SA/DP.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A744.

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Appendix A. Names of medications used in analyses and their corresponding Anatomical Therapeutic Classification (ATC) codes

Medication Name	**Anatomical Therapeutic Classification codes**
Paracetamol	N02BE01
NSAIDs	M01AB01-M01AX01
Nonselective	
• Diclofenac and diclofenac combinations	M01AB05, M01AB55
• Indometacin	M01AB01
• Sulindac	M01AB02
• Ketorolac	M01AB15
• Ibuprofen	M01AE01
• Naproxen	M01AE02
• Ketoprofen	M01AE03
• Dexibuprofen	M01AE14
• Piroxicam	M01AC01
• Tenoxicam	M01AC02
• Lornoxicam	M01AC05
• Mefanamic acid	M01AG01
COX-2 selective	
• Celecoxib	M01AH01
• Etoricoxib	M01AH05
• Meloxicam	M01AC06
• Nabumetone	M01AX01
Benzodiazepines	N05BA, N05CD
• Diazepam	N05BA01
• Oxazepam	N05BA04
• Potassium clorazepate	N05BA05
• Lorazepam	N05BA06
• Bromazepam	N05BA08
• Clobazam	N05BA09
• Aalprazolam	N05BA12
• Nitrazepam	N05CD02
• Flunitrazepam	N05CD03
• Triazolam	N05CD05
• Midazolam	N05CD08

Appendix A: Continued on the next page

Medication Name	**Anatomical Therapeutic Classification codes**
Antipsychotics	N05AA01-N05AB03,N05AB06-N05AL07,N05AX01-N05AX17
	N06AA01-N06AG02,N06AX01-N06AX11,N06AX13-N06AX26,
Antidepressants	N06AX12_1
	N02A
Opioids	
Weak opioids	N02AA59, N02AJ06, N02AJ07, N02AJ08, N02AJ09
• Combination codeine preparations	N02AC04
• Dextropropoxyphene	N02AX01
• Tilidine	N02AX02
• Tramadol	N02AD01
• Pentazocine	
Strong opioids	
• Morphine	N02AA01
• Hydromorphone	N02AA03
• Oxycodone	N02AA05
• Oxycodone/naloxone	N02AA55
• Ketobemidone	N02AB01
• Fentanyl	N02AB03
• Buprenorphine	N02AE01

NSAIDs, non-steroidal anti-inflammatory drugs.

*Where the ATC code has _1 at the end, the ATC code could be used for multiple indications and therefore to separate indication based on the item and product codes these additional digits were used.

Appendix B. Characteristics of opioid initiated

	All (n=201,641)	Weak opioid initiators (n=187,665)	Strong opioid initiators (n=13,976)
N(%) or mean ± standard deviation			
Type of opioid			
Weak opioid	187,665(93.1)	187,665(100)	0
Strong opioid	13,111(6.5)	0	13,111(93.8)
Both strong and weak opioid	865(0.4)	0	865(6.2)
Route of administration			
Oral	200,016(99.2)	186,915(99.6)	13,101(93.7)
Transdermal	651(0.3)	0	651(4.7)
Other	804(0.4)	690(0.4)	114(0.8)
≥Two routes	170(0.1)	60(0.0)	110(0.8)
Opioid dispensed			
Buprenorphine	709(0.4)	0	709(5.1)
Codeine combinations	87,026(43.2)	86,893(46.3)	133(1.0)
Dextropropoxyphene	30,042(14.9)	29,779(15.9)	263(1.9)
Fentanyl	123(0.1)	0	123(0.9)
Hydromorphone	<30	0	<30
Ketobemidone	1,109(0.6)	0	1,109(7.9)
Morphine	1,707(0.9)	0	1,707(12.2)
Oxycodone	10,428(5.2)	0	10,428(74.6)
Oxycodone/Naloxone	<30	0	<30
Tramadol	72,201(35.8)	71,728(38.2)	473(3.4)
Oral morphine equivalents (OMEs) in mg dispensed			
Total OMEs	364.1±450.5	351.0±426.0	540.3±676.7
Total OMEs <250	111,912(55.5)	106,994(57.0)	4,918(35.2)
Total OMEs 250-499	41,653(20.7)	37,731(20.1)	3,922(28.1)
Total OMEs 500-749	20,324(10.1)	17,890(9.5)	2,434(17.4)
Total OMEs 750-1000	21,491(10.7)	20,313(10.8)	1,178(8.4)
Total OMEs>1000	6,261(3.1)	4,737(2.5)	1,524(10.9)

Appendix C. Medications of interest dispensed in the 365 days prior to and including the date of opioid initiation

	All (201,641)	Weak opioid initiators (n=187,665)	Strong opioid (n=13,976)
Benzodiazepines[a]	13,297(6.6)	12,087(6.4)	1210(8.7)
Alprazolam	1,942(1.0)	1,797(1.0)	145(1.0)
Diazepam	5,357(2.7)	4,779(2.6)	578(4.1)
Flunitrazapam	612(0.3)	541(0.3)	71(0.5)
Nitrazepam	731(0.4)	678(0.4)	53(0.4)
Oxazepam	6,126(3.0)	5,635(3.0)	491(3.5)
Antidepressants	30,048(14.9)	27,781(14.8)	2267(16.2)
Antipsychotics	3,481(1.7)	3,193(1.7)	288(2.1)
Non-opioid analgesics	127,141(63.1)	115,379(61.5)	11,762(84.2)
Paracetamol	80,993(40.2)	70,693(37.7)	10,300(73.7)
NSAIDs[a]	89,282(44.3)	83,118(44.3)	6,164(44.1)
Selective COX-2 inhibitors	8,036(4.0)	7,245(3.9)	791(5.7)
Celecoxib	1,260(0.6)	1,045(0.6)	215(1.5)
Etoricoxib	5,386(2.7)	4,929(2.6)	457(3.3)
Nabumetone	1,299(0.6)	1,177(0.6)	122(0.9)
Nonselective NSAIDs	84,638(42.0)	78,941(42.1)	5,697(40.8)
Diclofenac	63,227(31.4)	59,047(31.5)	4,180(29.9)
Ibuprofen	11,976(5.9)	11,144(5.9)	832(6.0)
Dexibuprofen	2,418(1.2)	2,084(1.1)	334(2.4)
Naproxen	12,204(6.1)	11,532(6.1)	672(4.8)
Indometacin	416(0.2)	367(0.2)	49(0.4)
Tenoxicam	225(0.1)	195(0.1)	30(0.2)
Ketoprofen	3,893(1.9)	3,601(1.9)	292(2.1)

[a]Individual medications are presented only if n≥30 in all groups.

*The percentage under each medication class may be >100%, as an individual can have multiple medications within the same drug class.

Appendix D

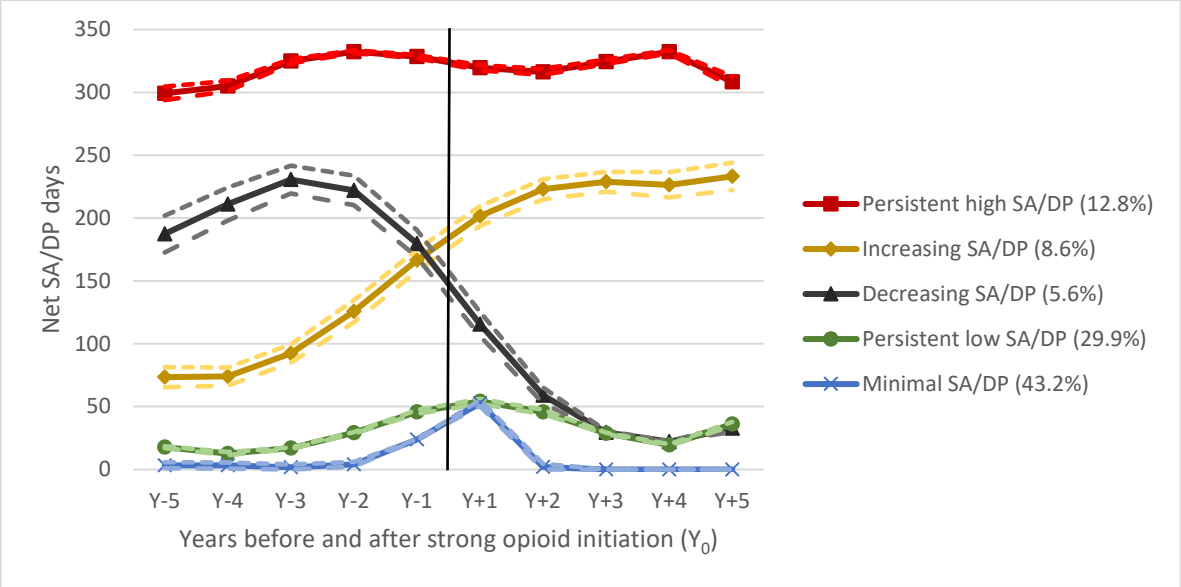

Figure D1 Sensitivity analyses of the five identified trajectories of net annual sickness absence (SA) and disability pension (DP) days among strong opioid initiators (n=13,007) 5 years before and 5 years after opioid initiation, excluding those who immigrated, died or emigrated during the study period. Date of opioid initiation (Y_0) is between Y-1 and Y+1 and is represented by the vertical line. For each trajectory, the solid lines represent the predicted trajectory and the broken lines represent the 95% confidence intervals. The legend indicates the percentage of the cohort belonging to each trajectory.

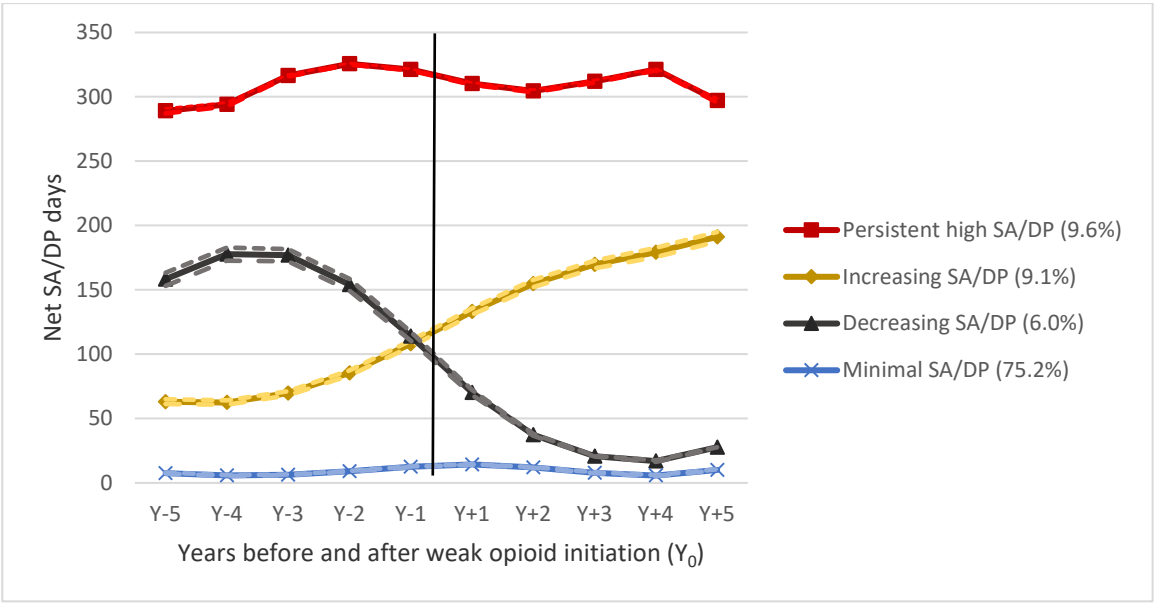

Figure D2 Sensitivity analyses of the four identified trajectories of net annual sickness absence (SA) and disability pension (DP) days among weak opioid initiators (n=177,173) 5 years before and 5 years after weak opioid initiation, excluding those who immigrated, died or emigrated during the study period. Date of opioid initiation (Y_0) is between Y-1 and Y+1 and is represented by the vertical line. For each trajectory, the solid lines represent the predicted trajectory and the broken lines represent the 95% confidence intervals. The legend indicates the percentage of the cohort belonging to each trajectory.

Chapter Seven – Discussion

7.1 Overview

Opioid analgesics play an integral role in the management of pain. However, an increase in opioid-related harm suggests that clinicians and consumers may not prescribe, dispense and administer opioids in accordance with the best available evidence. The quality use of opioids is important to achieve optimal outcomes and minimise harm. The work outlined in this thesis provides the foundation to better understand the patterns, predictors and outcomes of prescription opioid analgesic use. Harms and documented risk factors associated with extramedical prescription opioid analgesic use in Australia were explored using the scoping review methodology (Chapter Two).[242] This review provided important background information on the harms that have been reported in Australia and the corresponding data sources that have been used to investigate these harms. Initially, the review was intended to identify research gaps on the 'extramedical use' of opioids with a view to conducting original research on these topics. Research published by Blanch et al.[270] subsequent to my scoping review outlined challenges associated with defining extramedical opioid use in PBS data. Due to the challenges associated with defining extramedical use in PBS data, a comprehensive literature review on pain, patterns of opioid use and associated harm was conducted in Chapter One. This comprehensive review identified other patterns of opioid use that have also been identified as 'problematic' in the US and Canada. These include excess prescriptions, long-term, high-dose and high potency opioid use. These patterns provided the basis for the subsequent research conducted in this thesis.

Important gaps in the literature surrounding patterns of opioid use were identified. The prevalence, incidence, duration and dose of opioid use had not been investigated in Australia previously and could be investigated using the population-based individual-level PBS data. Chapter One also identified that sickness absence and disability are important outcomes to consider when investigating opioid use. This is because CNCP often affects an individual's short and long-term capacity to work[168] and sickness absence and disability are a major contributor of societal cost associated with CNCP.[47-50, 72, 170] However, the scoping review did not identify any

studies that assessed the impact of opioid use on SA/DP in Australia. This was largely because currently in Australia it is not possible to investigate this important outcome at a population level due to the inability to access or link national data. However, through international collaboration this question was addressed and has important implications for Australia. Various methodologies were employed throughout the thesis to investigate the following:

- The prevalence and incidence of prescription opioid analgesic use in Australia
- The characteristics of people with and without cancer initiating prescription opioid analgesic
- The trajectories of prescription opioid analgesic use and predictors of persistent prescription opioid analgesic use among people without cancer
- The rate and predictors of transition to strong and high-dose opioids
- The trajectories of SA/DP before and after strong and weak opioid initiation for non-cancer pain and the factors associated with these trajectories.

Findings from the research presented in this thesis have been published in pharmacy, clinical pharmacology and pain research journals. In the discussion and conclusion chapters, the overall findings from the thesis are discussed including their implications and the potential of this research to inform evidence-based strategies to improve opioid use and reduce opioid related harms in the future.

7.2 Discussion of main findings

7.2.1 Extramedical opioid use in Australia

Chapter Two[242] explored risk factors and harms associated with extramedical use of prescription opioid analgesics in Australia. This scoping review confirmed that harms associated with extramedical use of prescription opioid analgesics in Australia are similar to those in the US and Canada. Fatal and non-fatal overdoses were the most commonly reported harms in the peer-reviewed literature. Complex patterns of polysubstance use identified in the scoping review among people using opioids extramedically are consistent with findings in the US, Canada and Europe.[271-273] In Sweden, 41% of those who used prescription opioid analgesic extramedically in the past year also used illicit drugs.[271] Although parallels exist with the US and Canada, Europe and Australia appear to be in a position to avoid the scale of harm seen in the US and Canada. This is because the number of opioid-related overdose deaths[1, 181, 187] has not yet reached the levels seen in the US or Canada.[184, 274] Surveillance of extramedical opioid use and harm in Europe is somewhat limited as most data are from secondary sources, such as arrests, seizures, and drug treatment admissions.[271] Therefore the true prevalence of prescription opioid analgesic related harm is uncertain,[191, 271] but appears to be less than in the US and Canada.[181] Currently there is limited concern about harm from extramedical prescription opioid analgesic use in Europe.[181] Conversely, the surveillance of illict and extramedical drug use in Australia has provided signals for concern relating to harm associated with prescription opioid analgesic use and extramedical use.[1] Australia is still in a position to respond with targeted interventions because data already exist about strategies that have not been successful in the US and Canada. This provides an opportunity for Australia to focus on the strategies that have evidence for effectiveness, in combination with other strategies that may be suited to the Australian setting. This is important because there are clear differences in the health-care systems, illicit drug markets, policies and regulations that exist in Australia, Europe, Canada and the US.[55, 191]

The scoping review highlighted two main sub-populations where extramedical use of prescription opioid analgesics occurs in Australia. The first is among people who access prescription opioid

analgesics mainly for CNCP who do not have a history of substance dependence. The second is among individuals already dependent on illicit opioids or other substances. These findings are consistent with those identified in a population-based survey of extramedical opioid use in five European countries, including Sweden.[271] This survey identified two groups of people who use opioids extramedically; those who engage with polysubstance use and those that do not.[271] These findings suggest that extramedical use of prescription opioid analgesics in individuals with CNCP may arise due to suboptimal pain management, including inappropriate opioid analgesic prescribing. Polysubstance use, including concomitant use of benzodiazepines, antidepressants or other centrally-acting substances, was identified as a risk factor for harm in the scoping review. The scoping review also identified other risk factors for harms associated with extramedical opioid use. These included being male, aged between 30 and 49 years, having a history of CNCP, mental health disorders, and/or substance abuse. These risk factors were consistent with those identified in several studies.[260, 271, 275] The risk factors identified were used as variables in statistical models, where available, for investigating patterns and predictors of opioid use for the remaining pharmacoepidemiological studies included in this thesis. This was considered important because excess opioid use, long-term use and high-dose or potency investigated in Chapters Three to Five are also associated with increased opioid-related harm.[275] Therefore understanding how these 'problematic' patterns of opioid use relate to the risk factors for extramedical use and harm is important. Because the increase in opioid use has been mainly attributed to use for CNCP,[14-17] and this group was identified as at risk of opioid-related harm in the scoping review, this thesis focused primarily on opioid use among people without cancer. Using PBS data it was not possible to determine whether other illicit drugs were used concomitantly, however the use of other prescribed CNS-acting medicines was explored in Chapters Three to Six.

7.2.2 Patterns of opioid use in Australia

Chapters Three,[243] Four[244] and Five investigated three patterns of opioid use which have been identified as 'problematic' by the CDC due to their risk of addiction and overdose: 1) excess

prescriptions 2) long duration and 3) high doses.[29, 96] Chapter Three investigated the prevalence and incidence of opioid use in Australia. Chapter Four investigated long-term opioid use over a 12-month period and Chapter Five investigated the transition to high dose or strong-potency opioids. The findings from each study will be discussed in further detail below.

Chapter Three was the first national study to use individual-level data to investigate the prevalence and incidence of opioid use among adults in Australia between 2013 and 2017. This was important because previous PBS data did not capture under co-payment data and therefore estimating changes in prevalence and incidence of opioid use was difficult. This study identified that approximately 3 million adults use opioids and 1.9 million adults initiate opioids each year in Australia. The prevalence of opioid use increased by 0.6% over the study period, while the rate of opioid initiation decreased by 2.3% over the study period. The decline in opioid use appears to be similar to that seen in the US and Canada.[102, 108] Encouragingly, the amount of opioids dispensed on initiation, measured by total OMEs, did not increase between 2013 and 2017. However, over the same period the proportion of people initiating long-acting or strong opioids has increased. From our study it was unclear whether these changes in patterns of opioid use translated to a change in opioid-related harm. Subsequent to this research, the Australian Institute of Health and Welfare published a report investigating opioid harm in Australia and Canada.[1] This report highlighted that there are substantial and rising harms, including overdose deaths and hospitalisations, associated with both pharmaceutical and illicit opioids (e.g., heroin).[1] This report confirmed our findings that the use of strong opioids has increased.[1] Shortly after, the Society of Hospital Pharmacists of Australia released a report titled '*Reducing opioid-related harm: A hospital pharmacy landscape paper*' which supported the issues highlighted in our study about high rates of opioid use.[244] The report found that more than 70% of hospitals supply opioids frequently for patients to take home in the event that they may have pain, even if the opioids were not used in the 48 hours prior to discharge.[244] These reports and the findings that approximately 1 in 6 adults (16%) use opioids each year, support concern about excessive, potentially inappropriate prescribing, supply and use of opioids in Australia.

Chapter Three investigated the prescribing speciality of clinicians initiating opioids. This study identified that approximately half of all opioid initiations were by GPs. This is an important finding because in many states GPs do not have access to information regarding patient's previous prescriptions and dispensings from other prescribers. Timely access to patients' medicine histories is key as some patients may unknowingly or deliberately seek access to greater quantities of opioids than they need, placing them at increased risk of harm. Currently, there are two services that may help prescribers make informed prescribing decisions in Australia. One service is the national Prescription Shopping Programme (PSP)[276] and the other is a state-based real-time PDMP. Prescribers must contact the PSP information service to confirm their suspicion whether the patient is 'doctor shopping'.[276] The PSP has a high threshold of what constitutes 'doctor shopping' including that within 3 months a person must: 1) visit ≥6 prescribers; or 2) obtain ≥25 target PBS items (medicines); or 3) obtain any ≥50 PBS items (medicines).[276] If the patient meets these criteria, the prescriber can request a patient summary or get verbal advice on what the patient has had dispensed up to the last 24 hours.[276] If the patient does not meet the PSP criteria, the prescriber cannot obtain the patient's dispensing history unless the patient provides consent.[276] Anecdotal experience suggests that this service can be time-consuming, and may not identify many patients at risk of harm due to the strict threshold and not being available in real-time.

The second service available to help prescribers make informed prescribing decisions in Australia are real-time PDMPs. Currently, real-time PDMPs are only available in two states and one territory; Tasmania (DORA),[74] Victoria (SafeScript),[277] and Australian Capital Territory (DORA).[278] PDMPs provide real-time access to prescribers and pharmacist on patients dispensing history for certain high-risk medicines. DORA in Tasmania captures Schedule 4 and 8 opioids and all other Schedule 8 medicines,[74] while SafeScript currently captures all Schedule 8 medicine, all Schedule 4 opioids, and other high risk Schedule 4 medicines including benzodiazepines, z-drugs, and quetiapine.[277] DORA in Australian Capital Territory only captures Schedule 8 opioids. None of the PDMPs in Australia currently capture gabapentinoid use. Chapters Four and Five in this thesis

found that pregabalin use was associated with opioid persistence and transition to high-dose and strong opioid use. Other studies have also found that concomitant use of opioids and gabapentinoids was associated with an increased risk of opioid-related death.[128, 137-139] This may be a limitation of the Australian PDMP's. Although these programs appear to be useful clinically to help prescribers make more informed decisions, there has been mixed findings in the literature examining the impact of PDMPs and their effect on medicine use, extramedical use and harm.[222] The PDMPs are similar in terms of centralised state-wide data systems that electronically transmit prescription medicine data.[222] However, similar to the PDMPs in the US, the administrative features of PDMPs vary substantially among states and over time.[222] While changes in the incidence and prevalence of opioids across states was not compared in Chapter Three, sub-optimal use of opioids and harms associated with opioid use is not restricted to Tasmania and Victoria. Therefore, nationwide PDMPs are required in Australia to minimise the harm associated with prescription opioid analgesics.

Overall, Chapter Three investigated the first of three 'problematic' patterns of opioid use in Australia.[96] This chapter identified that people without cancer accounted for the majority of opioid initiations (98%). This was expected given that large increase in opioid use globally has been largely attributed to use in CNCP.[14-17] The initiation and use of prescription opioid analgesics is just one component of the complex picture of prescription opioid analgesic use. Understanding the longitudinal prescribing patterns, including duration and dose are equally important. Therefore, Chapter Three had implications for the next two studies in this thesis including determining how many people without cancer initiating opioids use them long-term and what doses they use over a 12-month period following initiation.

To further clarify the patterns of opioid use among people without cancer in Australia, in Chapter Four a retrospective cohort study of people initiating opioids was conducted. The study conducted found that 2.6% of adults initiating opioids become persistent users during a 12-month period. Extrapolating these results to the population level results from Chapter Three, approximately

50,000 adults who initiate opioids become long-term opioid users each year. In a study investigating two health plans in the US, 5.5% of people initiating opioids for CNCP used them long-term.[17] The definition for long-term use was based on ≥120 total days supply of dispensed medicine or ≥10 opioid prescriptions dispensed within a year.[17] A Canadian study found that 10% of individuals initiating opioids for non-cancer pain were using them long term (at least 6 months of opioid).[110] The study in Chapter Four, defined persistence over a longer period than the US and Canadian studies.[17, 110] Results vary considerably depending on the definition used for long-term or persistent opioid use.[109] A Norwegian study found that persistent opioid use can range from 1.3% (using a strict definition) to 9.8% (using a wider definition) among people initiating opioids, depending on the definition used.[109] Receiving a yearly total amount of opioids exceeding either 180 defined daily dose (DDD) or 4500 mg OMEs or both, in at least three out of four quarters of the year was the wide definition of persistence, while receiving ≥10 dispensings of opioids, distributed in all quarters of the year, and receiving a total amount of opioids exceeding 730 DDDs or 18 000 mg OMEs per year was the strict definition used.[109] The Norwegian study acknowledged that there is no single appropriate definition for persistent opioid use when using explicit criteria.[109] A key strength of the study in Chapter Four was that the definition of persistence using group-based trajectory modelling avoided the need for the use of explicit criteria.

Despite uncertainty about the benefits of long-term opioid analgesic use in the treatment of CNCP, there is clear evidence of harms, including dependence, drug diversion and non-fatal and fatal overdose.[14, 28, 111] While only a minority of people use opioids long-term in Australia, our knowledge about the long-term efficacy of opioid use is limited.[26] However, persistent use has been identified as a 'problematic' pattern of opioid use in CNCP due to increased risk of harm,[14, 28, 111] key predictors of persistent use at the time of opioid initiation were identified in Chapter Four. One important predictor for long-term opioid use was a history of mental health comorbidities. The presence of depression is a predictor of developing chronic pain and having chronic pain increases the risk of depression.[196] This complex bi-directional relationship between

depression and pain is well documented in the literature.[196, 279, 280] Interestingly, a study investigating patients presenting to an outpatient pain clinic found that people with depression were equally likely to be using opioids regardless of pain severity and were more likely to take them at higher levels of functioning compared to people without depression.[281] Mental health conditions, most commonly depression, were also identified as risk factors for harm in the scoping review in Chapter Two. The findings from these two studies are consistent with previous literature. A review by Sullivan concluded that '*Depression seems to function as a cause, as a consequence, and as a promoter of adverse reactions to long-term opioid therapy'*. This highlights the challenges faced by clinicians when considering prescribing opioids for CNCP. This is particularly complex considering that approximately 50% of people with chronic pain will have depression and vice versa.[185]

A retrospective-cohort study was conducted in Chapter Five to investigate the final 'problematic' pattern of opioid use according to the CDC, 'high dose'.[96] Chapter Five investigated the rate and predictors of transitioning to high-dose or strong opioids among people initiating opioids. In total, 7.3% of people who initiate weak opioids transition to strong opioids over the 12-months follow-up. Additionally, 1.4% of people who initiate opioids escalate to approximate doses ≥50 mg OMEs per day and 0.8% of people escalate to doses ≥90 mg OMEs per day over a 12-month period. People with cancer, older people and males transition to strong and high-dose opioids more rapidly. These results have direct clinical practice and health policy implications because high-dose opioid therapy is associated with substantial morbidity and mortality, including, falls, fractures, hospitalisation, motor vehicle accidents and opioid-related overdose and death.[14, 15, 116-118] People aged ≥75 years were at greatest risk of escalating to doses ≥50 mg OMEs per day and those aged between 55-74 years were at greatest risk of escalating to doses ≥90 mg OMEs per day. This is particularly concerning because in a cohort study of people aged ≥60 years with CNCP, high-dose opioid use (≥50 mg OMEs/day) was associated with a 10% annual fracture rate compared to no opioid use over the follow-up period.[117] This study investigated opioid use and average dose as a time-varying covariate among people with CNCP. Additionally, older people

are more susceptible to opioid-related adverse events, such as drowsiness, falls[201] and delirium,[264] due to pharmacokinetic and pharmacodynamic age-related changes.[263, 264] Our findings indicate that opioid prescribing patterns among older people need to be further investigated. Extrapolating our overall results to the population level results from Chapter Three, suggests that over 26,000 Australian adults initiating opioids escalate to high-doses each year. Additionally, more than one in every 13 people initiating weak opioids transition to strong opioids.

7.2.3 Sickness absence and disability pension among people initiating opioids

Chapter One identified the importance of function when considering the effect of the treatment modalities for CNCP management. Additionally, the indirect cost related to CNCP are the major constituents of the total cost related to CNCP. [47-50, 72, 170] Studies have also shown that opioids do not improve function among people with CNCP and may lead to prolonged disability and return to work.[171-180] Therefore, in addition to the gaps addressed on patterns, predictors and opioid-related harms in Chapters Two to Five, Chapter Six[269] set to explore the trajectories of work disability. Work disability measured by SA/DP days is a novel and important outcome to investigate because the high socioeconomic burden of CNCP is largely related to these indirect costs related to lost productivity.[105, 170] In Chapter Three, trajectories of opioid persistence in Australia were explored using PBS data. This data source does not include important sociodemographic or outcome variables. A study by Berecki-Gisolf et al[282] investigated work compensation claims (WorkSafe) in Victoria, Australia. Among injured workers, they found that 16% filled an injury-related opioid prescription within 2 years of the injury onset.[282] This dataset captures 85% of working age people in Victoria, however it is limited by the fact that an employer-paid excess of around $630 must be reached first before prescriptions appear in the dataset.[282] At the time of this thesis, it was not possible to examine nationwide work disability and opioid use in Australia. Therefore, I worked collaboratively with the Division of Insurance Medicine at the Karolinska Institute in Sweden to utilise their national linked registers to explore important sociodemographic variables and outcomes related to opioid initiation. Sweden was a logical choice because of the similarities with Australia including the health care system and access to opioids. Moreover, the Swedish linked registers have additional information compared to the PBS data alone including

the level of education, type of residence, SA and DP days. The linked nationwide data in Sweden were used to undertake the first longitudinal population-based study to investigate SA/DP trajectories before and after opioid initiation among people with non-cancer pain. This used the novel approach of group-based trajectory modelling to investigate SA/DP among people initiating opioids. Other studies investigating work disability and opioid use have used workers compensation data rather than nationwide data.[172, 173, 180] None of these studies used group-based trajectory modelling to investigate long-term patterns of work disability. However, group-based trajectory modelling has been used in other studies investigating SA/DP in the general population or specific patient populations.[229, 283-286] The key strength of this approach is that the patterns of SA/DP trajectory groups are defined by the data rather than pre-specified explicit criteria.[287]

In Chapter Six, three quarters of people initiating opioids were identified to have persistent low/minimal levels of SA/DP (estimated 30 days/year) in the five years before and after opioid initiation. It is possible that most of the opioid initiation in these trajectories was for acute rather than CNCP. Acute pain may resolve through opioid use, other treatment, or be self-limiting therefore having a minimal effect on SA/DP days/year long-term. Examples of such pain may include acute treatment of musculoskeletal pain, surgical pain, dental pain or pain resulting from a fracture. Although the majority of people had low SA/DP days/year, 12.5% of strong opioid initiators and 9.5% of weak opioid initiators had persistent high SA/DP days/year (estimated 320 SA/DP days/year). The high SA/DP days/year identified in Chapter Six is consistent with SA patterns observed among people with rheumatoid arthritis and osteoarthritis.[288] Given the high levels of SA/DP, it is likely that opioid use in this trajectory was for CNCP that is complex to manage. This is an important finding because CNCP is a leading cause of SA/DP and currently there is minimal evidence to support prescribing of opioids, particularly long-term, for CNCP. The patterns of SA/DP days/year identified for each trajectory group in Chapter Six appeared to reflect a continuation of the pre-initiation patterns. Based on these results, it appears that opioid initiation is not associated with a change in SA/DP at a population level. However, conclusions regarding

whether prescription opioid analgesic use for CNCP at an individual level facilitates or prolongs return to work cannot be made from this study.

Prior use of psychotropic medicines was strongly associated with higher SA/DP days/year among strong and weak opioid initiators. Similar to the findings in Chapters Two to Five, this study further supports the intricate bidirectional relationship between pain and depression and its association with persistently high SA/DP days/year. Additionally, higher age, more comorbidities, socioeconomic disadvantage, along with higher initial OMEs, were also factors strongly associated with higher SA/DP levels among people initiating weak or strong opioids. Our findings highlight the complex range of sociodemographic and medicine-related factors that are associated with persistent SA/DP. Interestingly, the factors that predicted persistent and high-dose opioid use in Chapters Four and Five were similar to those associated with higher SA/DP levels. Although the study in Chapter Six investigated people initiating opioids in Sweden, there are key similarities in pain prevalence, opioid access and health care systems that may help with generalisability to the Australian setting. The key findings that may be relevant to the Australian population is that the majority of people have low SA/DP days/year, but there is an important group that has persistent high levels of work disability. This group of people with persistent high SA/DP requires further investigation in both Sweden and Australia to determine other important outcomes including quality of life and mortality. Additionally, understanding the patterns of opioid use and other management strategies that have been trialled would be important in identifying preventative strategies to help reduce the risk of long-term disability.

7.3 Methodological strengths and limitations

Studies presented in this thesis investigated opioid use in two different health systems. There were methodological similarities and differences with the research conducted in Australia and Sweden. The research methods applied to the studies used similar definitions but various methodologies. Three of the studies utilised a 10% random sample of PBS data, one study utilised Swedish linked register data and one study was a review of existing literature. The

specific strengths and limitations relevant to each study have been described in further detail in Chapters Two through to Six. The strengths and limitations are now discussed more broadly, focusing on the data sources and methodologies used.

Strengths of the research presented in this thesis includes the use of a variety of statistical methods with common definitions that provided opportunities for analysis of various patterns of opioid use in Australia and Sweden. This included using the scoping review methodology to investigate harms related to extramedical use of opioids in Australia (Chapter Two). Scoping review methodology was selected because heterogeneity was anticipated in the data sources used, reporting of extramedical use of opioids and the harms reported. A strength of the scoping review methodology was that it provided the opportunity to ask a broad question and include research utilising heterogeneous study designs. A limitation of the scoping review methodology compared to systematic review methodology was that synthesis of findings is difficult. Rather it provided an opportunity to identify key themes and issues. However, the scoping review was still conducted in accordance with relevant sections of the PRISMA check-list[289] including quality assessment which is not commonly done in scoping reviews.[290] The scoping review set the scene for how the rest of the research would have implications on risk mitigations associated with opioid use.

This thesis was commenced at a time where data on all opioids subsidised by the PBS were captured in the PBS data source, providing us with a unique opportunity to provide an in-depth overview of prescription opioid analgesic use patterns in Australia which had not been previously studied. Opioid use was analysed from July 2012 in Chapters Three to Five because under co-payment prescription data was captured in the PBS data source form this time. This was important because some opioid prescriptions for general beneficiaries were under the co-payment threshold amount and, therefore, do not appear in the PBS data prior to July 2012. This meant that it was not possible to analyse individual or population level opioid use in Australia without restricting to people with a concessional status. The availability of this data was integral in

undertaking our individual and population-level research at a time where opioid-related harms were increasing.[1] Over the counter medicines purchased in pharmacies without prescription, private prescriptions (medicines not subsidised by the PBS), inpatient dispensing from all public hospitals and outpatient or discharge dispensing from public hospitals in New South Wales and the Australian Capital Territory are not captured by the PBS data. Over the counter codeine was available for purchase from a pharmacy during the inclusion dates of all studies included in this thesis. However, the PBS data is comprehensive capturing approximately 80% of all opioid use in Australia in 2014.[230]

In Chapter Four, group-based trajectory modelling was used to define persistence. This method avoids explicit definitions of persistence, instead, persistence was defined by the patterns of opioid dispensings for the cohort. This is important when investigating opioids as they have variable dosing and patterns of use. As discussed previously, there is no single appropriate definition for persistent opioid use when using explicit criteria.[109] The incidence and prevalence of persistent opioid use varies markedly depending on the definition used and the population investigated (e.g., among all patients initiating opioids compared to patients with chronic pain treated at a pain clinic). This makes it difficult to compare studies directly. Comparison of persistence across studies using group based trajectory modelling will not resolve the variability between populations in the studies but provides a method that defines persistence based on the patterns of opioid dispensing in the cohort studied. Consequently, there has been increasing interest in the application of group based trajectory modelling for persistence of medicines and outcomes that may have variable patterns over time.[291-293] This is because this method avoids explicit definitions for defining a pattern, rather the data defines the groups and the model assumes that the population is composed of distinct groups.[287] Group-based trajectory modelling was also applied in Chapter Six to determine the patterns of SA/DP days over a 10-year period in the Swedish population-based cohort of people initiating opioids. As discussed in section 7.2.3, none of the studies investigating opioid use and work disability used group-based

trajectory modelling to investigate long-term patterns of work disability.[172, 173, 180] However, group-based trajectory modelling has been used in other studies investigating SA/DP in the general population or specific patient populations.[229, 283-286] Similar to Chapter Four, the key strength of this approach is that the patterns of SA/DP trajectory groups are defined by the data rather than pre-specified explicit criteria.[287]

Chapter Six analysed Swedish national linked register data. Register data can be linked to different data sources using a unique personal identification number. This enables researchers to conduct longitudinal population-based analyses using linked data from a range of different data sources. The registers used in Chapter Six included the Swedish Prescribed Drug Register for medicine dispensing data and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) for sociodemographic variables. Data regarding SA and DP were obtained from the Micro Data for Analysis of the Social Insurance register. Details on cancer diagnosis were obtained from the Swedish Cancer Register, and date of death was extracted from the Cause of Death Register. Register linkage was performed using each individual's personal identification number. This is a unique 10-digit number assigned to all residents in Sweden. The Swedish linked data registers have been extensively used in research and provide comprehensive capture of widespread information relating to the Swedish residents.

As Chapters Three to Six were based on medicine dispensing databases, it is not known whether and how the medicine was taken. Data were not available on the use of non-pharmacological modalities for the management of pain. Additionally, in the absence of comorbidity data, dispensing data was used to identify treatment for specific medical conditions including cancer. Although RxRisk-V,[258, 259] a validated tool was used, there is a possibility that some people who have a particular condition may not have had medicines dispensed for that condition and were therefore not captured. The ability of the RxRisk index to predict mortality and identify specific medical conditions has been compared to the Charlson comorbidity index in a veteran population.[259] Neither index identified all medical conditions, but both indices were found to be

able to strongly predict mortality.[259] For some conditions including gastric, cardiovascular and respiratory diseases, the RxRisk index identified the majority of veterans with those conditions.[259] Cancer was not well identified by either index, 32.8% of people with cancer were identified by the RxRisk index and 56.8% with Charlson comorbidity index.[259] Hence, we developed a more comprehensive indicator of cancer to capture other antineoplastic therapies such as hormonal cancer therapies. This indicator was used throughout Chapters Three to Six. The use of linked Swedish data in Chapter Six permitted consideration of important sociodemographic characteristics, outcomes and prior medicine use not considered in previous studies. A strength of the linked register-based study was that it was not subject to recall error nor to dropout as information was available for all 10 years included in the study. Research in Chapters Three to Six was quantitative and did not use qualitative methods such as focus groups or interviews to explore and understand reasons behind extramedical opioid use.

7.4 Implications for consumers, clinicians and policy makers

The research presented in this thesis has a number of implications for consumers, clinicians and policy makers. Findings from this thesis have identified several key areas where further attention is required. These include a need to identify strategies to address excess opioid prescribing, long-term, high-dose, strong opioid and extramedical use, all of which have been associated with increased risk of opioid-related harm. The patterns of use identified in this thesis are similar to those seen in the US and Canada. However, Australia is currently in a position to avoid the large-scale 'opioid-crisis' seen in these countries. Given the complexities associated with prescription opioid analgesic use and extramedical use, achieving this will require large coordinated infrastructures and champions at the national, regional, state, and local levels. Public and health professional education about appropriate expectations in the management of pain and opioid analgesic use at all opioid access sites (e.g., community, hospital, outpatients) is vital for the harm-minimisation at every level. A recent report published by the Society of Hospital Pharmacists of Australia suggested services that could be implemented in hospitals to reduce inappropriate prescription opioid analgesic use.[244] Suggestions included: implementation of an

opioid analgesic stewardship service (concept based off antimicrobial stewardship), use of tapering or weaning opioid plans and clear and specific communication to general practitioners about opioid use on discharge.[244] Opioid initiation in hospital, particularly after surgery, occurs commonly and opioids are often given 'just in case' they are required.[244] From the findings in this thesis, it is also evident that prescribers in the community play a large part in opioid initiation and continuation in Australia. Further support and education is also required at the community level to ensure the safe, effective, appropriate and judicious use of prescription opioid analgesics occurs. This is a core component of how the NMP aims to achieve better health outcomes for all Australians.[227]

One of the challenges identified in the community is that clinicians may not be able to identify individuals at high risk of opioid-related adverse events. The My Health Record (MHR) system has recently been introduced in Australia. MHR is the Australian Government's digital health record system containing an online summary of an individual's health information.[294] It allows physicians, health care practitioners in hospitals, and other selected healthcare providers involved in an individual's care to view their health information. An individual can also access their My Health Record online. The aim of the MHR is to provide information to health care providers at the point of contact to facilitate continuity of care and provide safe and efficient care.[294] MHR allows individuals to choose whether to share their health information with their health care provider.[294] This may limit it's benefit for identifying extramedical opioid use. Nevertheless, MHR may enhance access to health information for some individuals at the point of care and provide health practitioners with medication prescribing and dispensing history which may assist with judicious prescribing and supply of opioids.

In the US, PDMPs have been implemented in almost every state to help clinicians identify individuals at high risk of opioid-related adverse events in the community. Real-Time PDMPs have been implemented in two states and one territory in Australia, Tasmania, Victoria and Australian Capital Territory.[74, 277, 278] Although this is a step in the right direction, there is a need

for a national PDPM and a national structured framework for safe and effective opioid use. The high and potentially risky patterns of opioid use identified in this thesis, support the calls for a national PDMP to help minimise the risk of opioid-related harm by providing health professionals timely access to prior dispensings of high-risk medicines. However, further evaluation of these programs is required to determine their impact on opioid use and opioid-related harm.

In addition to identification of individuals at increased risk of harm, treatment programs to help minimise harms need to be easily accessible. Additionally, prevention strategies that target the early stages of drug dependence should be developed. The likelihood of development of iatrogenic dependence needs to be discussed at the initiation of opioid treatment. Iatrogenic dependence can develop unintentionally after using opioids to treat a genuine medical issue. This can lead to extramedical use of opioids and significant opioid-related harm including those identified in the scoping review in Chapter Two.

7.5 Future research directions

This thesis identified several areas of potential future research to better understand and address the challenges associated with prescription opioid analgesic use for pain management, particularly in CNCP. In this thesis, two main data sources were used: PBS data and Swedish linked registry data. The scoping review in Chapter Two did not identify any published studies linking person-level data from multiple data sources that provided a comprehensive overview of the extent of extarmedical prescription opioid analgesic use and harms in Australia. Often, it was difficult to delineate medical and extramedical use of prescription opioid analgesics in the studies. This finding suggested that surveys or single data sources are commonly used to investigate extramedical opioid use in Australia. Identification of extramedical use through dispensing data has proven to be challenging as identified by Blanch et al.[270] This was because pain severity is difficult to determine based on dispensing claims alone and only the treating physician would

have all the information necessary to assess whether the volume of opioids obtained from visiting multiple doctors and pharmacies were for legitimate medical or extramedical purposes. However, linked data with physician or hospital medical records, and other data sources (e.g. opioid substitution therapy) could assist with identifying extramedical use and should be considered for future research.

The use of linked data for research purposes is well established in Sweden and other Nordic countries. Although studies utilising linked data are emerging in Australia, there are many challenges to its wide use. Nevertheless, Australia is in a unique position due to its universal healthcare system, large stores of routinely collected health data and capacity for linkage across disparate data collections. Several studies have used linked dispensing claim data with other health outcome datasets to examine the association between opioid use and harms in the US and Canada.[14-16, 116, 118, 295] Exploring opioid use and outcome in the general population through the use of linked data is required in Australia to comprehensively understand the nature and scale of the opioid problem. Currently there are no published Australian population-based studies using person-level linked data to examine individual patterns of prescription opioid analgesic use and outcomes. Future studies should link data from various sources to identify the extent of prescription opioid analgesic related harm, predictors of harm and interventions to minimise harm. Potential data linkage sources in Australia include Registrars of Births, Deaths and Marriages, National Coronial Information System, PDMP, National Hospital Morbidity Database, National Non-admitted Patient Emergency Department Care Database and Alcohol and Other Drug Treatment Services National Minimum Data Set.

The National Drug and Alcohol Research Centre in New South Wales will link the PBS data with a wide range of other datasets containing information on sociodemographic and clinical characteristics, health service use and adverse outcomes (e.g., opioid dependence and non-fatal and fatal overdose).[296] This project (POPPY II) is an extension of POPPY which investigated the patterns and costs of opioid use in Australia using PBS data alone.[297] POPPY II will provide

valuable information on the long-term outcomes of opioid use among adult residents in New South Wales who initiated prescribed opioids from 2002.[296] Opioid-related harms in Australia are not unique to New South Wales. There is a need for nationwide studies investigating harms associated with POA use, as there may be differences in incidence, prevalence and severity of harms across Australian states and territories.

There are many reasons why data linkage studies have not been performed in Australia in relation to opioid use. As mentioned throughout this thesis, under co-payment data for medicines has only been available since July 2012, making analysis of opioids prior to this time challenging. Additionally, there are challenges associated with linking data including legislative barriers, privacy concerns and the fragmented nature of health data collection.[298] Some data sources (e.g., hospital admissions) are under the custodianship of individual Australian States and Territories, while others (e.g., PBS data) are under the Commonwealth custodianship. Additionally, linkages of these various data sources are costly, resource intensive and time consuming. However, studies using linked data are necessary and would further help design and evaluate interventions to mitigate the risk of opioid-related harm. In 2009, the Population Health Research Network (PHRN) was established which is a network that enables existing health data from around Australia to be linked and made available for vital health and health related research purposes. A recent study investigated the use of linked data for health and human services research in Australia since the establishment of the PHRN.[299] This study found that the number of linked studies utilising PBS data has increased from 1% (n=1) in 2009-10 to 9% in 2010-11 (n=7).[299] Although this was a step in the right direction for conducting post-marketing medicine surveillance or evaluating medicine use and clinically important outcomes, the percentage remained relatively constant thereafter (9%, n=17 in 2016-17).[299] Additionally, thus far there have been no studies published investigating population-based individual level opioid use and clinically important outcomes (e.g., hospitalisation, death). The studies in this thesis were the first to identify 'problematic' patterns of prescription opioid analgesic use on an individual-level in the Australian

population. Further research is now required to determine whether changes in these patterns overtime result in changes in opioid-related harm.

This thesis has demonstrated that even over a 4-year study period opioid use has changed. Researchers should routinely re-examine dispensing claims data to determine if dispensing patterns shift due to real world events such as policy and regulation changes, listing of new opioid medicines and/or changes in the illicit drug supply and availability. Since codeine rescheduling in February 2018, all opioids are now only available via prescription in Australia. The effect of this regulatory change should be assessed in the future to determine the overall patterns of opioid use and harm since the change. However, low-dose codeine products (apart from aspirin/codeine 300/8mg) are not PBS listed and therefore will not be captured by the PBS data. Regardless, studies investigating opioid patterns or shifts would be important to investigate to determine the effect of rescheduling on clinically important outcomes. A study in the US investigated the effect of rescheduling hydrocodone to a more restrictive schedule as was the case in Australia with codeine. Jones et al[300] found that there were 26.3 million fewer hydrocodone combination product prescriptions dispensed in the year after rescheduling and an increase by 4.9% of non–hydrocodone combination product opioid analgesics in the 12 months after hydrocodone combination product rescheduling.[300] A similar study was conducted in Australia when alprazolam was rescheduled to Schedule 8.[301] Schaffer et al[301] also found that alprazolam prescribing reduced, while the use of other benzodiazepines increased. Interestingly, they found that the number of calls to the Poisons Information centre for alprazolam reduced and there was no change in the number of calls for other benzodiazepines.[301] These types of studies are important to evaluate the real-world effects of a policy change. The findings in this thesis indicate high opioid use on an individual and population level. However, the indication and clinical appropriateness of prescription opioid analgesics could not be determined. Identification of inappropriate prescribing could provide insight into targeted strategies to optimise opioid use. This is an important consideration for future studies as the common misperception is that strong opioids are more effective than weak opioids or non-opioid analgesics. This often results in

prescribing of opioids for the management of all types of moderate to severe pain. In fact, opioids are commonly prescribed in clinical practice for types of pain where their use has been shown to be ineffective or no more effective than non-opioid analgesics.[302-307] Identifying the indication and clinical appropriateness in future studies would be important for informing judicious and safe opioid prescribing.

Currently a limitation of the CDC Guideline for Prescribing Opioids for Chronic Pain guideline[29] is that it does not clearly detail how clinicians should manage patients currently prescribed doses that are in excess of 90mg OMEs/day. It is clear from our study in Chapter Five and similar studies in the US and Canada that there are people who are currently on doses above those recommended by the CDC guidelines.[308-310] These findings present opportunities for tapering or deprescribing of opioids. Although good quality evidence is limited investigating interventions for reducing or discontinuing long-term opioid therapy, it appears that patients receiving multimodal care which emphasises non-pharmacologic and self-management strategies may improve pain, function and quality of life.[311] Interventions implemented to reduce dose or deprescribe opioids among people on high-dose opioids should be investigated. This could inform the development of guidelines to assist clinicians with deprescribing of opioids to ensure effective and safe strategies that could be applied in clinical practice. Additionally, the effect of this strategy on opioid-related harm and pain management including assessment of quality of life and function needs to be investigated further. Furthermore, this bold vision will need champions at the national, regional, state, and local levels. Adequate funding, public and professional education will be necessary to achieve the aims of better care for patients with CNCP using multifaceted approaches including non-pharmacological management options. Additionally, further studies are required to determine the best management options for different types of chronic pain. These studies need to include clinically and societally important variables such as quality of life and return to work.

The findings in Chapter Six show that at a population level, opioid initiation did not seem to be associated with a change in pattern of SA/DP. Although people initiating opioids were followed

over time in Chapter Six, opioid use was assessed at baseline. Patterns of opioid use for individuals may vary over time. Future studies should investigate trajectories of opioid use and then the trajectories of SA/DP among people with various patterns of opioid use. Specifically, investigation of trajectories of dose or persistence over time in relation to work disability would provide important clinical insight to improve opioid-related outcomes. Additionally, trajectories of SA/DP among people with acute and CNCP should be investigated. This is important because these groups may have different patterns of SA/DP and opioid use. This type of research may provide more insight into the complexity of acute to chronic pain transition in regards to important outcomes such as function and quality of life rather than solely focussing on pain intensity.

Chapter Eight – Conclusion

Ensuring appropriate prescribing, dispensing and administration of prescription opioid analgesics is a daily challenge for clinicians and is associated with considerable societal costs and implications. There is widespread global concern about the increase in prescribing of opioid analgesics, extramedical use and harm. This thesis addressed several research gaps related to opioid use. The scoping review was the first synthesis of published peer-reviewed Australian literature on harms associated with extramedical use of prescription opioid analgesics. Based on the findings of the review, it can be concluded that extramedical use of opioids occurs in Australia and has been associated with a range of harms, including fatal and non-fatal overdose. Gaps exist in delineating medical and extramedical use and identifying signals in patterns of opioid use at the point of prescribing.

Consequently, three studies in this thesis utilised the PBS data to investigate patterns of prescription opioid analgesic use that have been identified internationally as ‘problematic’, but had not been studied previously in Australia. These patterns of prescription opioid analgesic use include excess prescribing, long-term and high-dose opioid use. This thesis confirmed that rates of opioid use remain high in Australia. One in six adults use prescription opioid analgesics and one in ten initiate prescription opioid analgesics each year in Australia. Of people without cancer who initiate opioids in Australia, 2.6% go on to become persistent users over a 12-month period. More than one in every 13 people initiating weak opioids transition to strong opioids and >26,000 Australian adults initiating opioids escalate to high-doses each year. Therefore, high rates of opioid use, persistent use, and high-dose and strong opioid use identified in this thesis, mirror use in the US and Canada, reinforcing concerns about opioid-related harms in Australia.

In addition to identifying ‘problematic’ patterns of prescription opioid analgesic use, an important and costly societal outcome was investigated in collaboration with colleagues from Sweden. This was the first study to identify that people initiating opioids have varying SA/DP days/year before

and after prescription opioid analgesic initiation and that these patterns reflect a continuation of pre-initiation patterns. These findings may support the limited role of opioids in CNCP, particularly in relation to improving return to work.

The overall findings of this thesis demonstrate how administrative data can be used as a powerful tool to provide insight into 'real-world' use of prescription opioid analgesics. The complex patterns of prescription opioid analgesic use identified in this thesis suggest that comprehensive and multi-level strategies are required to address opioid-related harm. Patient-centred, multifaceted strategies, with clearly defined and agreed upon expectations and goals of pain management, are crucial for safe opioid prescribing and use. While it is important to reduce harms associated with prescription opioid analgesic use, it is equally important that access is not prevented for people who may benefit from opioid treatment.

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Appendices

Appendix 1

Support letter from Dr Alexanderson, Karolinska Institutet

Appendix 2

The Honourable Geoffrey Connard AM Student Travelling Scholarship Award Letter

Appendix 3

Monash media report summary

Appendix 4

Media articles

Dept of Clinical Neuroscience
Division of Insurance Medicine

To
Dr Karen McConalogue
Manager, Research Programs
Faculty of Pharmacy and Pharmaceutical Sciences
Monash University
381 Royal Parade
Parkville VIC 3052
Australia

Dear Dr McConalogue,

I am writing this letter to confirm that we are happy to host Samanta Lalic at the Division of Insurance Medicine, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. During her research visit, Ms Lalic will undertake a research project investigating trajectories of sick leave after initiating opioid analgesics. We believe this collaboration will help strengthen the links between our respective universities as well as generate new important knowledge. We will provide her with a work space, computers, programs as well as the necessary data.

Yours sincerely,

[redacted]

Kristina Alexanderson
Professor, PhD, Division Head

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Berzelius väg 3, 6th floor
Solna

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MONASH University

Miss Samanta Lalic
Centre for Medicine Use and Safety
Faculty of Pharmacy and Pharmaceutical Sciences
Monash University

9 June 2017

Dear Samanta,

The Honourable Geoffrey Connard AM Student Travelling Scholarship

On behalf of the Board of the Faculty of Pharmacy and Pharmaceutical Sciences Foundation, I would like to congratulate you on your success in being awarded the Honourable Geoffrey Connard AM Student Travelling Scholarship for 2017.

The Honourable Geoffrey Connard made a generous gift of funds to the Foundation some time ago, with the express purpose to support talented research students. Geoffrey wanted to provide opportunities for students and early career researchers, such as yourself, to undertake travel to participate in international research placements or important conferences that would provide a different perspective for your work.

This Award will provide you with the unique opportunity to travel to Sweden and work with leading researchers at the Karolinska Institute, Solna. We understand that a 4 to 6-week placement will allow you to further investigate the harm associated with prescription opioid analgesic use.

The Connard Travelling Scholarship will provide funding (up to a maximum of $2000) to augment and support costs for international travel for the purposes of your research including any of the following:

- travel expenses (it is expected that you will travel economy class)
- accommodation
- conference registration (to a conference that the research theme regularly supports)
- research placement costs
- travel insurance
- any reasonable out of pocket living expenses.

Please note that the following conditions apply:

1. The money for the award will be allocated from the 2017 budget for travel planned this calendar year. If you need to carry forward any of the budget please contact the Faculty Research Office.
2. You are asked to provide a one-page written report or give a short presentation to the Faculty Graduate Research Committee upon return, outlining insights and new knowledge gained from the travel experience with a view to sharing this information more broadly with fellow research students and colleagues within your research theme. The report will be forwarded to the Faculty of Pharmacy and Pharmaceutical Sciences Foundation and made available for the Trustees of the Honourable Geoffrey Connard AM Student Travelling Scholarship.
3. You are expected to acknowledge the Trustees of the Honourable Geoffrey Connard AM Student Travelling Scholarship on publications, and posters and presentations at conferences, resulting from this award.

I wish you well in your research endeavours in Solna, Sweden, and I'm delighted that the generosity of the Honourable Geoffrey Connard AM will play a role in helping you achieve your research and career goals.

Congratulation and best wishes for your continued research investigations.

Yours sincerely,

Dr Karen McConalogue
Manager, Research Programs

Faculty of Pharmacy and Pharmaceutical Sciences
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19 NOV 2018

Media Report - Opioid Research

AM Radio

Interview with Samanta Lalic, Centre for Medicine Use and S...

Ross Stevenson and John Burns at 3AW, Melbourne, Breakfast on 19 Nov 2018 8:09 AM.

ASR: 6,922 AUD
Audience: 206,000 (126,000 female 16+ / 78,000 male 16+)
Duration: 3mins 00secs

Summary:
Interview with Samanta Lalic, Centre for Medicine Use and Safety, Monash University. Stevenson says Australia is in the midst of a prescription opioid epidemic and a new study shows that more than 1.9 million adults are starting to take the addictive drugs each year. Lalic says the data they used are all the data that is legally prescribed by the doctor and they don't have data on those who don't legally use them. Lalic says there's an overwhelming number of people who begin taking opioid each year. She says people often get prescribed for opioid for acute pain or chronic pain and these medications may not be the most effective medication for them. Lalic says a person can get high from using opioids and patients who use other medications illegally who are at high risk of this.

Interviewees:
- Samanta Lalic, Centre for Medicine Use and Safety, Monash University

Item Details:

- Item ID: X00076853733
- Location: Melbourne
- Region: VIC
- Type: AM Radio

A Monash University's Centre for Medicine Use and Safety re...

Newsreader at ABC Radio Brisbane, Brisbane, 07:45 News on 19 Nov 2018 7:55 AM.

ASR: 1,726 AUD
Audience: 53,700 (19,700 female 16+ / 33,000 male 16+)
Duration: 0mins 42secs

Summary:
A Monash University's Centre for Medicine Use and Safety research has discovered 1.9 million Australian adults start taking prescription opioids each year with thousands becoming long-term users. A similar study by the Australian Institute of Health and Welfare has reveals opioid-related deaths have nearly doubled in the last 10 years across the country.

Also broadcast from the following 10 stations:
ABC Capricornia (Rockhampton), ABC Far North (Cairns), ABC Gold Coast (Gold Coast), ABC North Queensland (Townsville), ABC North West Qld (Mt Isa), ABC Southern Queensland (Toowoomba), ABC Sunshine Coast (Sunshine Coast), ABC Tropical North (Mackay), ABC Western Queensland (Longreach), ABC Wide Bay (Bundaberg)

Item Details:
- Item ID: X00076854792
- Location: Brisbane
- Region: QLD
- Type: AM Radio

A Monash University's Centre for Medicine Use and Safety research has ...

Newsreader at ABC Radio Melbourne, Melbourne, 07:45 News on 19 Nov 2018 7:52 AM.

ASR: 2,937 AUD **Audience:** 132,000 (66,000 female 16+ / 62,000 male 16+)
Duration: 0mins 43secs

Summary:
A Monash University's Centre for Medicine Use and Safety research has discovered 1.9 million Australian adults start taking prescription opioids each year with thousands becoming long-term users. A similar study by the Australian Institute of Health and Welfare has reveals opioid-related deaths have nearly doubled in the last 10 years across the country. Overdoses from prescription medicines currently kill more Australians each year than road deaths and illicit drug overdoses.

Also broadcast from the following 8 stations:

ABC Ballarat (Ballarat), ABC Central Victoria (Bendigo), ABC Gippsland (Sale), ABC Goulburn Murray (Wodonga), ABC Mildura - Swan Hill (Mildura), ABC Shepparton (Shepparton), ABC South Western Victoria (Warrnambool), ABC Western Victoria (Horsham)

Item Details:
- Item ID: X00076854005
- Location: Melbourne
- Region: VIC
- Type: AM Radio

Research from the Centre of Medicine Use and Safety in Mo…

Newsreader at 3AW, Melbourne, 07:30 News on 19 Nov 2018 7:31 AM.

ASR: 2,928 AUD
Audience: 251,000 (135,000 female 16+ / 112,000 male 16+)
Duration: 0mins 40secs

Summary:
Research from the Centre of Medicine Use and Safety in Monash University suggests that Aus is on the verge of an opioid epidemic and the Therapeutic Goods Administration has called on both consumers and health professionals to control the situation.

Also broadcast from the following 14 stations:
2AY (Albury), 3BA FM (Ballarat), 3CS (Colac), 3NE (Wangaratta), 3SH (Swan Hill), 3WM (Horsham), 3YB (Warrnambool), Coast FM (Warrnambool), Light FM (Melbourne), Macquarie Sports Radio (Melbourne), Mixx FM Hamilton (Hamilton), Mixx FM Horsham (Horsham), SEN (Melbourne), TR FM (Traralgon)

Item Details:
- Item ID: X00076852936
- Location: Melbourne
- Region: VIC
- Type: AM Radio

A Monash University's Centre for Medicine Use and Safety research has …

Newsreader at ABC Radio Melbourne, Melbourne, 06:30 News on 19 Nov 2018 6:33 AM.

ASR: 1,454 AUD **Audience:** 84,000 (48,000 female 16+ / 32,000 male 16+)
Duration: 0mins 44secs

Summary:
A Monash University's Centre for Medicine Use and Safety research has discovered 1.9 million Australian adults start taking prescription opioids each year with thousands becoming long-term users. A similar study by the Australian Institute of Health and Welfare has reveals opioid-related deaths have nearly doubled in the last 10 years across the country. Overdoses from prescription medicines currently kill more Australians each year than road deaths and illicit drug overdoses.

Item Details:
- Item ID: X00076852671
- Location: Melbourne
- Region: VIC
- Type: AM Radio

A Monash University's Centre for Medicine Use and Safety research has ...

Newsreader at ABC Radio Melbourne, Melbourne, 05:30 News on 19 Nov 2018 5:33 AM.

ASR: 866 AUD **Audience:** 50,000 (22,000 female 16+ / 27,000 male 16+)
Duration: 0mins 44secs

Summary:
A Monash University's Centre for Medicine Use and Safety research has discovered 1.9 million Australian adults start taking prescription opioids each year with thousands becoming long-term users. A similar study by the Australian Institute of Health and Welfare has reveals opioid-related deaths have nearly doubled in the last 10 years across the country. Overdoses from prescription medicines currently kill more Australians each year than road deaths and illicit drug overdoses.

Item Details:
- Item ID: X00076852894
- Location: Melbourne
- Region: VIC
- Type: AM Radio

Research from Monash University's Centre for Medicine Use ...

Newsreader at ABC Radio Canberra, Canberra, 05:30 News on 19 Nov 2018 5:33 AM.

ASR: 116 AUD
Audience: 7,000 (5,000 female 16+ / 2,000 male 16+)
Duration: 0mins 42secs

Summary:
Research from Monash University's Centre for Medicine Use and Safety has found that 1.9 million Australian adults begin taking prescription opioids each year, with thousands becoming long-term users. Meanwhile, research from the Australian Institute of Health and Welfare says opioid deaths have nearly doubled in the last decade across Australia.

Item Details:
- Item ID: X00076851765
- Location: Canberra
- Region: ACT
- Type: AM Radio

Research by the Centre for Medicine Use and Safety at Mona...

Newsreader at 2GB, Sydney, 05:30 News on 19 Nov 2018 5:31 AM.

ASR: 1,855 AUD
Audience: 123,000 (66,000 female 16+ / 58,000 male 16+)
Duration: 0mins 40secs

Summary:
Research by the Centre for Medicine Use and Safety at Monash University found 1.9 Australian adults begin taking prescription opioids every year. Meanwhile, deaths involving opioids have doubled in Australia over the last decade and has overtaken deaths caused by road deaths and illicit drug overdose. Therapeutic Goods Administration called for consumers and health professionals to provide input in strategies to address high rates of opioid prescribing.

Also broadcast from the following 13 stations:
2BS (Bathurst), 2CC (Canberra), 2EC (Bega), 2GN (Goulburn), 2LT (Lithgow), 2MAX (Narrabri), 2QN (Deniliquin), 2XL (Cooma), 2YOU FM (Tamworth), Coast FM (Gosford), Great Lakes FM (Taree), Macquarie Sports Radio (Sydney), Magic 2CH (Sydney)

Item Details:
- Item ID: X00076851759
- Location: Sydney
- Region: NSW
- Type: AM Radio

FM Radio

Research by Monash University has found 1.9 m Aussie adul...

Newsreader at Triple J, Sydney, 08:00 News on 19 Nov 2018 8:01 AM.

ASR: 46,713 AUD
Audience: 221,000 (79,000 female 16+ / 127,000 male 16+)
Duration: 0mins 43secs

Summary:
Research by Monash University has found 1.9 m Aussie adults begin taking prescription opioid each year. According to a research published by the Centre for Medicine Use and Safety, patients are being prescribed stronger initial doses compared to previous years. Similar research by the Australian Institute of Health and welfare shows deaths regarding the substance have nearly doubled in the 10 years.

Also broadcast from the following 7 stations:
Triple J (Perth), Triple J (Melbourne), Triple J (Canberra), Triple J (Brisbane), Triple J (Adelaide), Triple J (Hobart), Triple J (Darwin)

Item Details:
- Item ID: X00076854041
- Location: Sydney
- Region: National
- Type: FM Radio

A new Monash University study has found Australia is in a prescription …

Newsreader at NOVA 100.3, Melbourne, 07:30 News on 19 Nov 2018 7:36 AM.

ASR: 697 AUD **Audience:** 117,000 (64,000 female 16+ / 28,000 male 16+)
Duration: 0mins 12secs

Summary:
A new Monash University study has found Australia is in a prescription opioid epidemic.

Item Details:
- Item ID: X00076853122
- Location: Melbourne
- Region: VIC
- Type: FM Radio

A Monash University study reveals Australia is in the midst of a prescrip…

Newsreader at NOVA 100.3, Melbourne, 06:00 News on 19 Nov 2018 6:02 AM.

ASR: 125 AUD **Audience:** 21,000 (12,000 female 16+ / 5,000 male 16+)
Duration: 0mins 12secs

Summary:
A Monash University study reveals Australia is in the midst of a prescription opioid epidemic.

Item Details:
- Item ID: X00076853584
- Location: Melbourne
- Region: VIC
- Type: FM Radio

Newspaper

Pain drug epidemic

Ryan On at Courier Mail(page 1) on 19 Nov 2018.

ASR: 4,092 AUD **Audience:** 135,007

View Original **View Full Text**

Item Details:
- Item ID: 1038742968
- Section: General News
- Location: Brisbane
- Region: QLD
- Classification: Capital City Daily
- Format: 233 cm² News Item
- Words: 341
- Type: Newspaper

Painkiller addiction soars

Ryan On at Courier Mail(page 3) on 19 Nov 2018.

ASR: 3,688 AUD **Audience:** 135,007

View Original **View Full Text**

Item Details:
- Item ID: 1038790610
- Section: Edition Changes - Metro
- Location: Brisbane
- Region: QLD
- Classification: Capital City Daily
- Format: 210 cm² News Item
- Words: 296
- Type: Newspaper

Painkiller script surge

Cairns Post(page 3) on 19 Nov 2018.

ASR: 361 AUD **Audience:** 13,896

View Original **View Full Text**

Item Details:
- Item ID: 1038768893
- Section: General News
- Location: Cairns
- Region: QLD

- Classification: Regional
- Format: 72 cm² News Item
- Words: 147
- Type: Newspaper

A nation addicted to opioids

Ryan On at Daily Telegraph(page 8) on 19 Nov 2018.

ASR: 3,355 AUD **Audience:** 232,067

View Original **View Full Text**

Item Details:
- Item ID: 1038734518
- Section: General News
- Location: Sydney
- Region: NSW
- Classification: Capital City Daily
- Format: 71 cm² News Item
- Words: 117
- Type: Newspaper

Our opioid epidemic

Ryan On at Herald Sun(page 12) on 19 Nov 2018.

ASR: 11,494 AUD **Audience:** 303,140

View Original **View Full Text**

Item Details:
- Item ID: 1038714687
- Section: General News
- Location: Melbourne
- Region: VIC
- Classification: Capital City Daily
- Format: 207 cm² News Item
- Words: 318
- Type: Newspaper

Epidemic of opiod addiction

Ryan On at Hobart Mercury(page 4) on 19 Nov 2018.

ASR: 600 AUD **Audience:** 28,265

View Original **View Full Text**

ls:
38760716
neral News
Hobart
- Region: TAS
- Classification: Capital City Daily
- Format: 83 cm² News Item
- Words: 159
- Type: Newspaper

Online News

Opioid epidemic has reached Australia: study

miragenews.com on 19 Nov 2018 12:10 AM.

ASR: 1,094 AUD **Audience:** N/A

Item Details:
- Item ID: 1038737203
- Words: 437
- Location: Online
- Type: Online News

Opioid epidemic has reached Australia: study

Medianet on 19 Nov 2018 12:07 AM.

ASR: 1,079 AUD **Audience:** N/A

Item Details:
- Item ID: 1038736292
- Words: 427
- Type: Online News

Monash University researchers find Australians increasingly ...

Ryan Tennison at Townsville Bulletin on 19 Nov 2018 12:00 AM.

ASR: 1,048 AUD **Audience:** N/A

Item Details:
- Item ID: 1038742074
- Words: 365
- Location: Online
- Type: Online News

Monash University researchers find Australians increasingly ...

Ryan Tennison at Geelong Advertiser on 19 Nov 2018 12:00 AM.

ASR: 58 AUD **Audience:** N/A

Item Details:
- Item ID: 1038742193
- Words: 365
- Location: Online
- Type: Online News

Monash University researchers find Australians increasingly ...

Ryan Tennison at Daily Telegraph Australia on 19 Nov 2018 12:00 AM.

ASR: 233 AUD
Audience: 27,344 unique visitors per day / 361 average story audience

Item Details:
- Item ID: 1038742072
- Words: 365
- Location: Online
- Type: Online News

Monash University researchers find Australians increasingly ...

Ryan Tennison at Cairns Post on 19 Nov 2018 12:00 AM.

ASR: 6 AUD
Audience: 947 unique visitors per day / 14 average story audience

Item Details:
- Item ID: 1038742248
- Words: 365
- Location: Online

- Type: Online News

Monash University researchers find Australians increasingly ...

Herald Sun on 19 Nov 2018 12:00 AM.

ASR: 1,508 AUD
Audience: 37,109 unique visitors per day / 1,055 average story audience

Item Details:
- Item ID: 1038738567
- Words: 357
- Location: Online
- Type: Online News

Monash University researchers find Australians increasingly addicted to...

Brisbane Courier-Mail on 19 Nov 2018 12:00 AM.

ASR: 60 AUD
Audience: 15,056 unique visitors per day / 115 average story audience

Item Details:
- Item ID: 1038742203
- Words: 365
- Location: Online
- Type: Online News

Monash University researchers find Australians increasingly ...

Ryan Tennison at Gold Coast Bulletin on 19 Nov 2018 12:00 AM.

ASR: 291 AUD
Audience: 3,376 unique visitors per day / 30 average story audience

Item Details:
- Item ID: 1038742254
- Words: 365
- Location: Online
- Type: Online News

Monash University researchers find Australians increasingly ...

Adelaide Now on 19 Nov 2018 12:00 AM.

The Advertiser

ASR: 66 AUD
Audience: 11,799 unique visitors per day / 111 average story audience

Item Details:
- Item ID: 1038757650
- Words: 365
- Location: Online
- Type: Online News

Social Networks

Almost 2 million Australian adults begin taking prescription ...

shpa

@SHPA at Twitter on 19 Nov 2018 10:13 AM.

Followers: 3,530 **Following:** 1,411 **Tweets:** 3,530

Item Details:
- Item ID: DS0076383331
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America's opioid epidemic is starting to hit Australia's shores

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Sciences

There's no such thing as a typical drug addict. The stereotype paints them as depraved, corrupt degenerates and criminals, but this fails to acknowledge that people from all walks of life battle this brain disease, or that too many die as a result of their addiction.

Indeed, there's increasing opposition to the terms 'drug addict' and 'drug abuser', as they're considered pejorative, stigmatising and reinforce the notion that the person is to blame.

A report by the Global Commission on Drug Policy last year called for an urgent change in language, one that frames addiction as a health issue and not a personal and moral inadequacy.

Similarly, the stereotype of a typical drug overdose needs to be challenged. It's not just the heroin user, destitute and young, slumped over and unconscious in an inner-city alleyway.

The reality is more mainstream, suburban and regional. The reality is also white-collar and includes the misuse of prescription medications, in particular pharmaceutical opioids such as OxyContin, on a huge scale.

And it's a reality being felt across the developed world.

Escalating use of opioids in America has been described as one of the worst drug epidemics in the country's history. Its Centers for Disease Control and Prevention (CDC) estimates that more than 115 Americans die every day after overdosing on opioids, and that emergency room visits and deaths related to opioid overdose have more than tripled in the past 15 years, and continue to rise.

In 2016, more than 63,000 people in America died from drug overdoses – more than 42,000 of those involved prescription or illicit opioids.

Three waves

This rise in opioid overdose deaths in America came in three waves, according to the CDC. The first, in the 1990s, coincided with an increase in prescription opioids. The second wave, in 2010, showed a rapid increase in heroin overdose deaths, following restrictions in prescription opioid supply. The third, around 2013, was driven by a significant increase in overdose deaths associated with illicitly manufactured synthetic opioids, such as fentanyl, which have contaminated illicit opioid supplies.

Health authorities, police and the Trump administration in October last year declared it the biggest health emergency facing the nation.

"As Americans, we cannot allow this to continue," President Trump said. "It's time to

liberate our communities from this scourge of drug addiction."

Australia hasn't been spared, with increasing opioid-related harms also beginning to sweep across its shores.

According to the Australian Bureau of Statistics, a drug-induced death in 2016 was "most likely to be a middle-aged male, living outside of a capital city who is misusing prescription drugs such as benzodiazepines or oxycodone in a polypharmacy [the use of multiple drugs] setting".

"The death was most likely to be an accident," it said.

Professor Dan Lubman is the director of Turning Point, Australia's national addiction treatment and research centre, as well as director of the Monash Addiction Research Centre at Monash University. He's acutely aware of the developing opioid crisis here.

"There's no doubt we're headed for a crisis," he said. "What's happening in America is a tragedy, with almost 1000 opioid-related deaths every week, and if we don't respond appropriately, we will be on a similar trajectory here."

Growing evidence of harm

Opioids are one of the main types of medications used to treat acute severe pain, and are commonly prescribed after surgery or an injury . Although they're also commonly used to treat chronic pain conditions such as back pain, there's no research to support their use long-term, and growing evidence that they actually are harmful.

Common naturally derived opioids available legally by prescription include codeine, morphine and oxycodone. Synthetic opioids available by prescription include pethidine, fentanyl and tramadol.

It's also a class of drug that includes heroin.

Opioids work by binding to and activating opioid receptors on cells located in the brain, spinal cord and other organs in the body, especially those involved in feelings of pain and pleasure. When opioids attach to these receptors, they block pain signals sent from the brain to the body and release large amounts of dopamine, which can lead to a feeling of euphoria.

A grim picture

A new report from the Australian Institute of Health and Welfare (AIHW) paints a grim picture of rapidly increasing opioid overdoses and misuse.

In its report *Opioid harm in Australia: and comparisons between Australia and Canada*, the institute says the number of deaths in Australia involving opioids has nearly doubled in the decade to 2016, from 591 to 1119. The rate of hospitalisation where opioid poisoning was recorded as the main reason for admission rose by 25 per cent during the same period.

"Every day in Australia, there are nearly 150 hospitalisations and 14 presentations to emergency departments involving opioid harm, and three people [a day] die from ... opioid use," AIHW spokeswoman Dr Lynelle Moon says.

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In 2016, the most common types of opioids responsible for deaths were naturally derived opioids (oxycodone, codeine and morphine), which were attributed to 550 deaths, followed by heroin (361 deaths).

In 2016-17, 15.4 million opioid prescriptions were dispensed under the Pharmaceutical Benefits Scheme (PBS) to 3.1 million people. Oxycodone was the most commonly dispensed prescription opioid (5.7 million), followed by codeine (3.7 million) and tramadol (2.7 million).

Oxycodone is prescribed to treat severe pain, and includes brands such as Endone and OxyContin. Codeine and tramadol are used to treat milder pain.

Need to raise awareness

Samanta Lalic is a Monash University PhD student who's analysed the dispensing of opioids through the PBS between 2013 and 2017.

Her research, conducted through the Centre for Medicine Use and Safety at the University's Faculty of Pharmacy and Pharmaceutical Sciences, found that 1.9 million Australian adults begin taking prescription opioids every year and that 2.6 per cent of them – around 50,000 – become long-term users.

The research was recently published in the British Journal of Clinical Pharmacology.

Ms Lalic said the medical community needed to change its prescribing culture regarding opioids.

"Opioids do have an important role in managing cancer pain and acute non-cancer pain; however, their use remains less well-established for chronic non-cancer pain," she said.

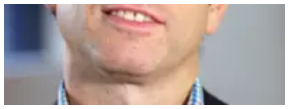
"For the treatment of chronic pain, we need to raise the levels of awareness of other treatment options among patients. In many cases, the safest and most effective way to treat chronic pain involves a combination of therapies, including exercise, physiotherapy and non-opioid painkillers."

OPIOIDS | DRUG ADDICTION | OXYCONTIN | DAN LUBMAN | SAMANTA LALIC | OVERDOSE

Featuring

Dan Lubman

Dan has worked across mental health and drug treatment settings in the UK and Australia. His research includes investigating the harms associated with alcohol, drugs and gambling, the impact of alcohol and drug use on brain function, the relationship between



substance use, gambling and mental disorder, as well as the development of targeted telephone, online and face-to-face intervention programs within school, primary care, mental health and drug treatment settings.

Samanta Lalic

PhD Candidate at the Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences

Samanta is a PhD Candidate at the Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences. Samanta is also a clinical pharmacist at Austin Health. Her clinical practice and research are focussed on the quality use of medicines. Samanta's thesis is focussed on investigating patterns and harms of opioid analgesic use.

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NEWS

A SNAPSHOT OF OPIOID USE

MEGAN HAGGAN 19/11/2018

New PBS data shows that opioid prevalence in Australia has increased since 2013, but incidence

has decreased

And in response, pain stakeholders have called for better access to multi-disciplinary treatments, as well as compassion for those in pain.

The study, published in the *British Journal of Clinical Pharmacology*, aimed to determine both prevalence and incidence of prescription opioid analgesic use in Australia, and also to compare the characteristics of people with and without cancer initiating prescription opioid analgesics.

The researchers, from the Centre for Medicine Use and Safety (CMUS) at the Monash University Faculty of Pharmacy and Pharmaceutical Sciences, analysed opioid dispensing through the PBS from 2013 to 2017.

The retrospective population-based study used a random 10% sample of adults receiving such scripts.

"Opioid prevalence increased {RR = 1.006 [95% confidence interval (CI) 1.004, 1.008]}, while incidence decreased [RR = 0.977 (95% CI 0.975,0.979)] from 2013/2014 to 2016/2017," the authors write.

"There were between 287,677 and 307,772 prevalent users each year. In total, 769,334 adults initiated opioids between 2013/2014 and 2016/2017, and half of these initiations were by general practitioners.

"Initiation with a strong opioid occurred in 55.8% of those with cancer and 28.2% of those without cancer."

The study concluded that rates of opioid use remain high, with around three million adults using the medicines, and more than 1.9 million adults initiating opioids each year.

"Between 2013 and 2017, opioid prevalence has slightly increased but incidence has decreased," the authors write.

"People without cancer account for the majority of opioid use and are more likely to be initiated on short-acting and weak opioids. Initiation of strong opioids has increased over time, reinforcing concerns about increased use and the harms associated with strong opioids in the community."

Concerning findings

Lead author Samanta Lalic, who is an Austin Health pharmacist and CMUS PhD candidate, said that of particular concern was the finding that 2.6% of Australians (around 50,000 people per year) become long-term users over a year.

Also of concern was that an increasing proportion of patients are being started on stronger opioids, she said.

According to Ms Lalic, this a significant worry because both long-term use and the use of strong opioids are associated with a range of adverse health outcomes: overdose deaths, falls, fractures, hospitalisations and motor vehicle accidents.

“Opioids do have an important role in managing cancer pain and acute non-cancer pain. However, their use remains less well established for chronic – i.e. long-term – non-cancer pain,” Ms Lalic said.

“For the treatment of chronic pain, we need to change prescribing culture and raise the level of awareness of other treatment options among patients. The goal of care, treatment expectations and intended duration should be agreed upon by patients and prescribers prior to opioid initiation.

“In many cases the safest and most effective way to treat chronic pain will involve a combination of therapies, including exercise, physiotherapy and non-opioid painkillers.”

Ms Lalic said the next step is to determine how prescribers and patients escalate doses over time.

Approaching pain with compassion

Commenting on the study, Chronic Pain Australia said that it believes the most effective way to manage chronic pain is through a multi-disciplinary approach, which may include medication where appropriate.

“While we all might want every person living with chronic pain to regularly see their GP, pharmacist, pain specialist, physiotherapist, counsellor and other health practitioners, the reality is that this is not affordable for most people living with chronic pain,” said Chronic Pain Australia National President Dr Coralie Wales.

“If we want to see all Australians living with chronic pain take a multi-disciplinary approach to managing their pain, then we need to ensure that it is affordable for them. How do we realistically expect people to be able to change the way they manage their pain?”

Dr Wales also encouraged people reading the report to consider the daily struggles confronting someone living with chronic pain.

"I think it is important that we bring back compassion for people living with chronic pain when we discuss issues like opioids in their treatment. It is very important for people to try and view the situation from the perspective of someone living with chronic pain," said Dr Wales.

Dr Wales also said that while opioids need to be used appropriately for the treatment of chronic pain, this does not meant they should be withheld if prescribed opioids is the best option to treat and manage a person's chronic pain.

Pharmacist Jarrod McMaugh, who is on Chronic Pain Australia's board, told the AJP that "Opioids have a place in treatment of pain, and that a decision to NOT use them should be based solely of therapeutic appropriateness at the discretion of the clinician."

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Is Australia next in line for an opioid class action?

AAA

BY KATE ALLMAN - JUN 04, 2019 7:00 AM AEST

The US opioid epidemic has been described as the worst drug crisis in American history. Australia has so far evaded the damage that has led to an historic class action against opioid manufacturer Purdue Pharma. But as opioid use increases in Australia, how far are we from a similar action?

They're the American-British family worth more than most of Hollywood put together. But despite their estimated US$13 billion net wealth, most people have never heard of the Sackler family. Until recently.

Lawyers around the world sat up to pay attention in February 2019, when one of the world's largest-ever class actions was brought against members of this formerly secretive, multi-billion-dollar dynasty.

epidemic through aggressive marketing tactics that vastly underestimated the addictive qualities of OxyContin.

And while the American crisis and ensuing legal battle may seem far removed from Australia, a leading consumer rights and class action lawyer says an opioid-related class action could well be "in the wind for Australia".

"If a person develops a crippling addiction from a drug prescribed for common pain problems, and they've relied on representations that said it was not addictive, then they can claim damages for misleading and deceptive conduct," says Ben Slade, Managing Principal of Maurice Blackburn in Sydney and head of the firm's NSW class actions department.

"They may also be able to claim for personal injury under Australian Consumer Law, depending on the extent of the addiction and the harm caused."

The monumental US action has since been split into some 2,000 lawsuits filed in various federal and state courts against Purdue Pharma, some joining other drug makers as defendants. The first of these suits, brought against Purdue and the Sacklers by the US state of Oklahoma, was settled for US$270 million (AU$378 million) in April.

"If the evidence is that the impact of drugs is as severe as the Americans allege – people becoming chronically addicted and unable to keep working, losing their jobs and income – it could well be that a class action is in the wind for Australia," says Slade.

The impending opioid crisis

Opioids and in particular OxyContin, which generated an estimated US$35 billion in sales between 1996 and 2017, have become synonymous with a plague of addiction that has ravaged American communities since prescription opioids became available in the 1990s. Prior to this crisis, heroin was the drug most commonly involved in overdose deaths. (Heroin itself is a type of opioid and induces a similar pain-relieving "high".) But deaths from prescription opioids like oxycodone and morphine have increased sixfold since 1999, according to the US Centers for Disease Control and Prevention. Overdose death rates involving both licit and illicit opioids skyrocketed by 137 per cent between 2000 and 2016. And the US Council on Foreign Relations estimates that more than 900 Americans die from opioid-related overdoses every week.

Australia hasn't escaped this crisis. Local academics like Samanta Lalic, a clinical pharmacist and PhD candidate at Monash University, are increasingly warning of the opioid-related harm sweeping our shores. Lalic is part of a team conducting the first ground-breaking research into the growth of prescription opioid use in Australia. The team's first alarming findings were published in the *British Journal of Clinical Pharmacology* in 2018.

"We found that one in six Australian adults use opioids every year – which was a huge number when you think about it," says Lalic. "We also found that one in 10 start taking opioids each year.

"To put it another way, 1.9 million Australian adults initiate opioid use, and 3 million use opioids each year."

BEN SLADE, NSW MANAGING PRINCIPAL, MAURICE BLACKBURN

If the evidence is that the impact of drugs is as severe as the Americans allege – people becoming chronically addicted and unable to keep working, losing their jobs and income – it could well be that a class action is in the wind for Australia.

Lalic says dependant users are often first exposed to prescription painkillers for chronic conditions like back pain. They need stronger doses as the pain persists and they grow accustomed to the medication. If they hit obstacles sourcing legal prescriptions, they might turn to illegal opiods. Heroin is a common progression.

"People assume that the stereotype of a drug user or 'addict' is the depraved, criminal, homeless junkie or druggie," says Lalic. "But what we have actually seen is that it can be anyone who initiates opioid use and becomes dependant. The reality is more mainstream, suburban, white-collar and regional."

White-collar workers and middle-aged, suburban mums and dads are among the thousands of Americans who have transitioned from prescription opioids to heroin and lost their livelihoods in the process. These are the types of victims claiming compensation from Purdue Pharma and the Sackler family. Although many Australians may associate drug overdose death with young people living in cities, Australia's annual overdose report 2018 by the Penington Institute found that almost 70 per cent of accidental overdose deaths occur in middle-aged Australians between 30-59.

A class action in Australia?

Despite the disturbing data trends, Lalic thinks an opioid-related class action like those being mounted against the Sackler family is less likely to be successful in Australia. She says the aggressive marketing campaigns that Purdue Pharma embarked on to distribute OxyContin in the US have not been replicated here. Australian plaintiffs might find it harder to pin fault on the manufacturer.

"In Australia we have different laws and regulations regarding advertising of drugs," says Lalic. "We are a lot stricter. Opioids cannot be advertised on TV, whereas in America it's a sort of free-for-all so any medications can be advertised."

But Slade believes a legal argument could be mounted based on a lack of acceptable quality of goods, required by the Competition and Consumer Act.

OxyContin is a popular brand of oxycodone, a pain-relieving prescription opioid.

"Australian Consumer Law has specific provisions for compensation for injury caused via products or goods that have been bought," he explains. "If a product is provided that is not acceptable quality and it causes injury, then one has a claim to compensation for the injury it has caused. The threshold is that the injury must have an impact on you that is greater than 15 per cent of total bodily injury."

Slade notes that Maurice Blackburn ran a successful class action relating to medical goods in 2016, against DePuy and Johnson & Johnson Medical for manufacturing defective hip implants. In that case, 2,000 applicants settled with the companies for AU$250 million.

"If a drug company fails to warn you about addiction risks of taking drugs, and you become addicted, and that addiction is so crippling that it's regarded as imposing an injury on you of greater than 15 per cent of total bodily injury, you can claim," says Slade.

"If you then lose your employment, you will have an economic loss associated with that. Serious crippling addictions will do that."

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