

***What is normal?***

***A critical analysis of the methods quantifying prescription drug use  
and potential misuse in pharmaceutical claims***

**Bianca Blanch**

**Bachelor of Liberal Studies (Hons)**

**Masters of Criminology**

Thesis by published works

A thesis submitted in partial fulfilment of requirements for the degree of  
Doctor of Philosophy

**Faculty of Pharmacy**

**The University of Sydney**

November 2016

## ***Statement of originality***

This thesis describes research carried out at the Faculty of Pharmacy, University of Sydney under the supervision of Professor Sallie-Anne Pearson, Professor Nicholas Buckley, Professor Paul Haber and Professor Andrew Dawson.

This is to certify to the best of my knowledge, the work presented in this thesis is original except as acknowledged in the text. This thesis has not been submitted, either in full or in part, for the award of any degrees or any other purposes. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.



**Bianca Blanch**

**PhD candidate**

## ***Abstract***

The overall objective of this body of work is to examine methods of quantifying prescription drug misuse in pharmaceutical claims. We approach this by first undertaking a systematic review of the global literature measuring the extent of prescription drug misuse in pharmaceutical claims. Our review highlights four measures, based on number of prescribers, number of dispensing pharmacies, volume of drug dispensed and number of early refills, are used frequently to define prescription drug misuse. Despite this homogeneity, we found heterogeneity in the thresholds delineating use from misuse and a lack of established or validated benchmarks to accurately measure misuse in pharmaceutical claims. In our empirical work, we focus on prescription opioid analgesics due to the recent and considerable global increase in use and opioid-related harms. We use publically available, routinely collected data to document increases in prescription opioid use and related harms in Australia over 20-years. Over three chapters we then explore population norms of prescription drug access in national dispensing claims and examine how these access patterns relate to the metrics defining 'misuse' identified in our systematic review. We compare prescription drug access in Australia and British Columbia, Canada, for prescription opioids and statins, drug classes with high or no known abuse potential, respectively. We found access norms are remarkably similar across drug classes and healthcare settings. However, extreme access patterns are more common in people dispensed opioids, younger age groups or those receiving income assistance. We then examine opioid access in Australian adults initiating or reinitiating strong opioid treatment. We found the standard metrics defining 'misuse', including doctor and pharmacy shopping, are non-specific in that they identify misuse, but are also likely to capture high-need patient

groups including individuals with a history of cancer treatment. From a translational perspective, our findings are particularly important as the US Food and Drug Administration recently endorsed using routinely collected data, including pharmaceutical claims, to quantify prescription opioid misuse and measure the effectiveness of interventions aimed to curb the 'opioid epidemic'. We recommend using these commonly established metrics with caution due to their inability to isolate a population of people misusing opioids.

## ***Data and ethics approval***

Chapters One, Two, Three and Eight did not require any data access or ethics approvals. For Chapters Four through Seven, data access was approved by the Australian Government Department of Human Services External Review Evaluation Committee (reference numbers: MI0166; MI2593; MI2779) and ethics approvals were granted from the Population and Health Services Research Ethics Committee (reference numbers: 2013/11/494; 2013/10/481).

## ***Acknowledgements***

I would not have finished this PhD without the support of many inspirational individuals.

First and foremost, to my supervisor Professor Sallie-Anne Pearson; words cannot express my supreme gratitude for all of the support, time, energy, tough love and laughter you provided throughout my PhD. I have grown tremendously as a person and a researcher under your tutelage. I am also extremely appreciative for the insightful 'clinician view' provided by Professor Nicholas Buckley and the support of my other supervisors Professor Andrew Dawson and Professor Paul Haber. I would also like to thank all of my collaborators, particularly the POPPY group, for always questioning my assumptions, I have learned so much from all of you. To put it simply, this PhD would not be what it is without your contributions.

I am also grateful for the support of my friends and family who always asked about the PhD and never looked bored when I responded; particularly to my husband, Phillip Dunn, who has loved and supported me unconditionally throughout all of my university studies and my sister, Juanita Glavimans. Also, to my friends, who became my impromptu PhD support group, specifically Danijela Gnjidic, Jen Nicholas, Liesbeth Geerligs, Emily Karanges, Kat Fletcher and Peta Croker.

I would also like to acknowledge the financial support provided by the University of Sydney Scholarships Office and the Centre of Research Excellence in Medicines and Ageing (1060407).

## ***Publications arising from this thesis***

PhD peer-reviewed journal articles (thesis chapter order):

1. **Blanch B**, Buckley NA, Mellish L, Dawson AD, Haber PS, Pearson S. Harmonizing post-market surveillance of prescription drug misuse: a systematic review of observational studies using routinely collected data (2000-2013). *Drug Safety*. 2015; 38(6): 553-564.
2. **Blanch B**, Pearson S, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *British Journal of Clinical Pharmacology*. 2014; 78(5): 1159-1166. Award: *British Journal of Clinical Pharmacology editors' pick 2014*.
3. **Blanch B**, Gladstone E, Smolina K, Buckley NA, Karanges EA, Morgan SG, Pearson S. Benchmarking prescription drug access patterns in dispensing claims: a method for identifying high and potentially harmful opioid use in Australia and Canada. Under consideration for publication; peer-reviewed twice by *Journal of Pharmaceutical Health Services Research*; responded to reviewers' comments 7 November, 2016.
4. Degenhardt L, **Blanch B**, Gisev N, Larance B, Pearson S. The POPPY Research Programme protocol: investigating opioid utilisation, costs and patterns of extra-medical use in Australia. *BMJ Open*. 2015; 5: e007030.

5. **Blanch B**, Degenhardt L, Buckley NA, Gisev N, Dobbins T, Karanages EA, Larance B, Larney S, Pearson S. Prescription opioid access patterns and factors associated with increasing number of prescribers, pharmacies and dispensings: an observational study using pharmaceutical claims. Under consideration for publication; peer-reviewed by *Pain Medicine*; responded to reviewers' comments 20 October, 2016.
  
6. **Blanch B**, Daniels B, Litchfield M, Pearson S. Looking forward and looking back: the balancing act in new drug user designs for pharmacoepidemiological research. *Pharmacoepidemiology and Drug Safety*. 2015; 24: 1117-1119.

*See Appendices A-D for journal formatted published manuscripts.*

At time of submission, four of these chapters were accepted for publication in international, peer-reviewed journals. The 2016 impact factor for the publishing journals ranged from 2.3 to 3.9; three journals had an impact factor equal to or greater than *Pharmacoepidemiology & Drug Safety* (IF: 2.9), the leading international pharmacoepidemiology journal.

Other peer-reviewed articles published during my PhD candidature (chronological order):

1. Mellish L, Karanges EA, Litchfield MJ, Schaffer AL, **Blanch B**, Daniels BJ, Segrave A, Pearson S. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Research Notes*. 2015; 8: 634.
  
2. Karanges EA, **Blanch B**, Buckley NA, Pearson S. Twenty-five years of prescription opioid use in Australia: a whole of population analysis using pharmaceutical claims. *British Journal of Clinical Pharmacology*. 2016; 82(1): 255-267. Award: Australian and

*New Zealand Health Services Research Association's best paper written by an early career researcher.*

3. Gisev N, Pearson S, **Blanch B**, Larance B, Dobbins T, Larney S, Degenhardt L. Initiation of strong prescription opioid analgesics in Australia: cohort characteristics and factors associated with the type of opioid analgesic initiated. *British Journal of Clinical Pharmacology*. 2016; 82(4): 1123-1133.

*See Appendices E-G for journal formatted manuscripts.*

All conference presentations occurring during my PhD candidature (chronological order):

1. **Blanch B**, Mellish L, Buckley NA, Dawson AH, Haber PS. How is prescription opioid misuse measured, and what is the extent of opioid misuse globally? A systematic review of observational studies using routinely collected dispensing data (2000-2013). Global Addiction Conference; Rio de Janeiro, Brazil; 10-12 November 2014; oral presentation.
2. **Blanch B**, Srasuebkul P, Pearson SA. Prescribed opioid misuse in Australia: measurement in routinely collected dispensing data. Global Addiction Conference; Rio de Janeiro, Brazil; 10-12 November 2014; poster presentation.
3. **Blanch B**. What is the extent of prescribed medicine misuse globally using routinely collected data? University of Sydney Faculty of Pharmacy Annual Postgraduate Conference; Sydney, Australia; 28 November 2014; oral presentation.

4. **Blanch B**, Buckley N, Srasuebkul P, Litchfield M, Pearson SA. Prescription opioid use and potential misuse in Australia (2006-2013). 31<sup>st</sup> International Conference on Pharmacoepidemiology & Therapeutic Risk Management; Boston, United States of America; 23-26 August 2015; poster presentation. Published abstract: *Pharmacoepidemiology and Drug Safety*. 2015; 24(1): 157-158.
5. Daniels B, **Blanch B**, Litchfield M, Pearson SA. Relative misclassification of new medicine users in pharmacoepidemiological research: the impact of look-back periods. Population Health Congress; Tasmania, Australia; 4 October 2014; oral presentation.
6. **Blanch B**. How can we measure prescription opioid misuse using routinely collected data? University of Sydney Faculty of Pharmacy Annual Postgraduate Conference; November 2015; Sydney, Australia; oral presentation. *Award: Runner up for Best Presentation*.
7. **Blanch B**. Potential pitfalls in defining prescription opioid misuse using routinely collected dispensing data: 'doctor shopping' or standard care? 9<sup>th</sup> Health Services and Policy Research Conference; December 7-9 2015; Melbourne, Australia; oral presentation. *Award: Emerging researcher best abstract*.
8. **Blanch B**, Degenhardt L, Gisev N, Dobbins T, Larance B, Larney S, Pearson S (2016). Prescription opioid access patterns in Australia: a national observational cohort study. 31<sup>st</sup> International Conference on Pharmacoepidemiology & Therapeutic Risk

Management; Dublin, Ireland; 25-28 August 2016; poster presentation. Published abstract: *Pharmacoepidemiology and Drug Safety*. 2016; 25(Sup 3): 216-217.

9. Gisev N, Pearson S, **Blanch B**, Larance B, Dobbins T, Larney S, Degenhardt L. Initiation of strong prescription opioids in Australia: cohort characteristics of factors associated with the type of opioid initiated. 31<sup>st</sup> International Conference on Pharmacoepidemiology & Therapeutic Risk Management; Dublin, Ireland; 25-28 August 2016; poster presentation. Published abstract: *Pharmacoepidemiology and Drug Safety*. 2016; 25(Sup 3): 212-213.

10. Gisev N, Pearson S, **Blanch B**, Larance B, Dobbins T, Larney S, Degenhardt L. Characteristics of a population-based cohort initiating strong prescription opioids in Australia and factors associated with the type of opioid initiated. National Drug and Alcohol Research Centre Annual Symposium; Sydney, Australia; September 2016. Poster presentation.

*See Appendices H-N for accepted/published conference abstracts.*

#### Research awards and honours (chronological order)

1. *British Journal of Clinical Pharmacology* 'Editors' pick 2014'. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *British Journal of Clinical Pharmacology*. 2014; 78(5): 1159-1166.

<http://onlinelibrary.wiley.com/doi/10.1111/bcp.12587/full>

2. 'Runner up for Best Presentation' at University of Sydney Faculty of Pharmacy 2015 Annual Postgraduate Conference; November 2015; Sydney, Australia.
  
3. 'Emerging Researcher Best Abstract' at 9<sup>th</sup> Health Services and Policy Research Conference; December 2015; Melbourne, Australia.
  
4. Australia and New Zealand Health Services Research Association's 'Best Paper Written by an Early Career Researcher' in 2016.

## ***Student declaration of contribution***

The PhD candidate led all of the projects presented in this thesis, except Chapter Five which was a collaborative project. Specifically, the nature and extent of the candidate's contribution to each piece of work presented in this thesis includes:

	<b>Contribution to study concept and design</b>	<b>Statistical analysis</b>	<b>Interpretation of data</b>	<b>Writing first draft of manuscript</b>	<b>Critical review of manuscript</b>	<b>Final approval of manuscript</b>
<b>Chapter One</b> <i>Introduction</i>	A	N/A	A	A	A	C
<b>Chapter Two</b> <i>Systematic review</i>	C	A	C	A	C	C
<b>Chapter Three</b> <i>Opioid trends</i>	C	A	C	A	C	C
<b>Chapter Four</b> <i>Access patterns – Australia and Canada</i>	C	C	C	A	C	C
<b>Chapter Five</b> <i>POPPY protocol</i>	C	N/A	N/A	C	C	C
<b>Chapter Six</b> <i>POPPY access patterns</i>	C	A	C	A	C	C
<b>Chapter Seven</b> <i>Look-back periods</i>	C	C	C	A	C	C
<b>Chapter Eight</b> <i>Discussion</i>	A	N/A	A	A	A	C

A: PhD candidate completed this task alone; C: PhD candidate led this task but it was completed in collaboration with PhD supervisors and co-authors; N/A: not applicable, as no data was presented in this chapter/publication

We deem the above table is a true and accurate depiction of the PhD candidate's contribution to the work presented in this thesis.



*Signature of PhD candidate: Bianca Blanch*



---

*Signature of supervisor: Prof. Sallie-Anne Pearson*

## ***Table of contents***

<b>WHAT IS NORMAL? .....</b>	<b>1</b>
<b>A CRITICAL ANALYSIS OF THE METHODS QUANTIFYING PRESCRIPTION DRUG USE AND POTENTIAL MISUSE IN PHARMACEUTICAL CLAIMS.....</b>	<b>1</b>
<b>STATEMENT OF ORIGINALITY.....</b>	<b>II</b>
<b>ABSTRACT .....</b>	<b>III</b>
<b>DATA AND ETHICS APPROVAL.....</b>	<b>V</b>
<b>ACKNOWLEDGEMENTS.....</b>	<b>VI</b>
<b>PUBLICATIONS ARISING FROM THIS THESIS .....</b>	<b>VII</b>
<b>STUDENT DECLARATION OF CONTRIBUTION .....</b>	<b>XIII</b>
<b>TABLE OF CONTENTS .....</b>	<b>XV</b>
<b>LIST OF TABLES.....</b>	<b>XXI</b>
<b>LIST OF FIGURES .....</b>	<b>XXIV</b>
<b>LIST OF ABBREVIATIONS .....</b>	<b>XXVI</b>
<b>CHAPTER ONE: INTRODUCTION.....</b>	<b>1</b>
1.1 PRESCRIPTION DRUG USE .....	3
1.2 PRESCRIPTION OPIOID ANALGESICS.....	3
1.2.1 <i>What is an opioid?</i> .....	3
1.2.2 <i>Brief history of opium to opioid use</i> .....	4
1.2.4 <i>Pain</i> .....	5
1.2.5 <i>Prevalence and burden of pain</i> .....	6
1.2.6 <i>Global opioid consumption</i> .....	6

1.3 PRESCRIPTION OPIOID TREATMENT GUIDELINES.....	9
1.4 PRESCRIPTION OPIOIDS: BENEFITS AND RISKS.....	10
1.4.1 <i>Benefits of prescription opioid treatment</i> .....	11
1.4.2 <i>Risks of prescription opioid treatment</i> .....	13
1.5 PRESCRIPTION OPIOID-RELATED HARMS .....	14
1.5.1 <i>Recreational opioid use</i> .....	15
1.5.2 <i>Opioid harms</i> .....	15
1.5.3 <i>Economic impact of opioid misuse</i> .....	16
1.6 REAL WORLD METHODS OF QUANTIFYING PRESCRIPTION OPIOID MISUSE.....	17
1.6.1 <i>Structured clinical interviews</i> .....	18
1.6.2 <i>Questionnaires</i> .....	19
1.6.3 <i>Medical chart review</i> .....	20
1.6.4 <i>Routinely collected data</i> .....	21
1.7 AUSTRALIA.....	23
1.7.1 <i>Pain: prevalence and economic burden</i> .....	23
1.7.2 <i>Rates of non-medical prescription drug use</i> .....	24
1.7.3 <i>Australian healthcare system</i> .....	24
1.7.4 <i>Australian Pharmaceutical Benefits Scheme (PBS)</i> .....	24
1.7.5 <i>National Pharmaceutical Drug Misuse Strategy</i> .....	30
1.7.6 <i>Australian prescription opioid research using pharmaceutical claims</i> .....	30
1.8 REFERENCES.....	32

## **CHAPTER TWO: HARMONISING POST-MARKET SURVEILLANCE OF PRESCRIPTION DRUG**

### **MISUSE: A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES USING ROUTINELY**

#### **COLLECTED DATA (2000-2013)..... 53**

KEY POINTS..... 54

ABSTRACT..... 55

2.1 INTRODUCTION .....

2.2 METHODS.....	58
2.2.1 Eligible studies.....	58
2.2.2 Study identification.....	58
2.2.3 Data extraction.....	59
2.2.4 Terminology.....	61
2.2.5 Analysis.....	61
2.3 RESULTS.....	62
2.3.1 Studies identified.....	62
2.3.2 Study features.....	62
2.3.3 Measures of prescription drug misuse.....	67
2.3.4 The extent of prescription drug misuse.....	68
2.3.5 Factors associated with prescription drug misuse.....	72
2.3.6 Justification of measures of misuse.....	72
2.3.7 Comprehensiveness of reporting observational studies.....	73
2.4 DISCUSSION.....	73
2.4.1 Reporting recommendations.....	76
2.5 CONCLUSIONS.....	77
2.6 REFERENCES.....	79

## **CHAPTER THREE: AN OVERVIEW OF THE PATTERNS OF PRESCRIPTION OPIOID USE, COSTS**

<b>AND RELATED HARMS IN AUSTRALIA .....</b>	<b>91</b>
KEY POINTS.....	93
ABSTRACT.....	94
3.1 INTRODUCTION.....	96
3.2 METHODS.....	98
3.2.1 Setting.....	98
3.2.2 Data sources and method.....	98
3.2.3 Prescribed opioid use and costs.....	99
3.2.4 Opioid-related hospitalisations.....	100

3.2.5 Accidental poisoning deaths .....	101
3.3 RESULTS .....	102
3.3.1 Prescribed opioid use and costs .....	102
3.3.2 Opioid-related harms .....	104
3.3.3 Accidental poisoning deaths .....	106
3.4 DISCUSSION.....	106
3.4.1 Cost of opioid utilisation .....	109
3.4.2 Opioid-related harms .....	110
3.5 CONCLUSIONS.....	112
3.6 REFERENCES .....	113

**CHAPTER FOUR: BENCHMARKING PRESCRIPTION DRUG ACCESS PATTERNS IN DISPENSING CLAIMS: A METHOD FOR IDENTIFYING HIGH AND POTENTIALLY HARMFUL OPIOID USE IN AUSTRALIA AND CANADA? .....** **119**

KEY POINTS.....	121
ABSTRACT.....	122
4.1 INTRODUCTION .....	124
4.2 METHODS.....	125
4.2.1 Study design .....	125
4.2.2 Settings .....	125
4.2.3 Data sources .....	125
4.2.4 Prescription drugs of interest.....	127
4.2.5 Cohort inclusion criteria .....	127
4.2.7 Statistical analysis.....	128
4.3 RESULTS .....	128
4.3.1 Cohort demographics.....	128
4.3.2 Number of unique prescribers.....	132
4.4 DISCUSSION.....	138

4.5 CONCLUSIONS.....	142
4.6 REFERENCES.....	143

**CHAPTER FIVE: THE POPPY RESEARCH PROGRAM PROTOCOL: INVESTIGATING OPIOID**

**UTILISATION, COSTS AND PATTERNS OF EXTRAMEDICAL USE IN AUSTRALIA..... 153**

KEY POINTS.....	154
ABSTRACT.....	155
5.1 INTRODUCTION.....	157
5.2 METHODS.....	159
5.2.1 <i>Setting</i> .....	159
5.2.2 <i>Opioids of interest</i> .....	160
5.2.3 <i>Data of interest</i> .....	160
5.2.4 <i>Statistical analysis</i> .....	163
5.2.5 <i>Data access approval</i> .....	167
5.2.6 <i>Consent and privacy considerations</i> .....	168
5.2.7 <i>Confidentiality of data and record retention</i> .....	169
5.3 DISCUSSION.....	170
5.3.1 <i>Limitations</i> .....	171
5.4 CONCLUSIONS.....	172
5.5 REFERENCES.....	173

**CHAPTER SIX: PRESCRIPTION OPIOID ACCESS PATTERNS AND FACTORS ASSOCIATED WITH INCREASING NUMBER OF PRESCRIBERS, PHARMACIES AND DISPENSINGS: AN**

**OBSERVATIONAL STUDY USING PHARMACEUTICAL CLAIMS..... 184**

ABSTRACT.....	185
6.1 INTRODUCTION.....	187
6.2 METHODS.....	188
6.2.1 <i>Setting</i> .....	188
6.2.2 <i>Data source</i> .....	188

6.2.3 Prescription opioids of interest .....	189
6.2.5 Study measures .....	191
6.2.6 Statistical analysis.....	194
6.2.7 Ethics approval.....	195
6.3 RESULTS .....	196
6.3.2 Opioid use and access patterns.....	198
6.4 DISCUSSION.....	208
6.5 CONCLUSIONS.....	210
6.6 REFERENCES .....	211
<b>CHAPTER SEVEN: LOOKING FORWARD AND LOOKING BACK: THE BALANCING ACT IN NEW DRUG USER DESIGNS FOR PHARMACOEPIDEMOLOGICAL RESEARCH.....</b>	<b>220</b>
KEY POINTS.....	222
7.1 REFERENCES .....	228
<b>CHAPTER EIGHT: DISCUSSION.....</b>	<b>229</b>
8.1 KEY FINDINGS AND FUTURE RESEARCH DIRECTIONS .....	230
8.1.1 Limitations of the traditional threshold approach to quantify prescription drug misuse .....	230
8.1.2 Pharmaceutical claims in quantifying misuse: limitations and future potential.....	231
8.2 EXAMINING DRUG ACCESS PATTERNS AND HARM.....	233
8.2.1 Data linkage and datasets .....	233
8.3 GAPS IN PHARMACEUTICAL BENEFITS SCHEME DATA .....	237
8.4 IMPLICATIONS FOR POLICY AND PRACTICE .....	239
8.4.1 Australian prescription drug monitoring programs .....	242
8.5 CONCLUSIONS.....	245
8.6 REFERENCES .....	247
<b>APPENDIX A: CHAPTER TWO SUPPLEMENTARY MATERIAL.....</b>	<b>254</b>

## **List of Tables**

<b>Table 2.1</b> Characteristics of included studies.....	64
<b>Table 2.2</b> Summary of measures with a defined threshold of prescription drug misuse .....	69
<b>Box 2.2</b> Recommendations for observational studies investigating prescription drug misuse .....	78
<b>Table 3.1</b> The number of opioids available in Australia for prescription.....	97
<b>Table 4.1</b> Cohort demographics.....	130
<b>Table 4.2</b> Three most frequently dispensed prescription drugs by class and jurisdiction (2011) .....	131
<b>Table 4.3.</b> Comparison of unique number of prescribers by prescription drug class and age group in Australia and British Columbia (2011).....	134
<b>Supplementary Table 4.1</b> Publically subsidised opioid analgesics and statins included in analysis by jurisdiction .....	147
<b>Supplementary Table 4.2</b> Distribution of number of unique statin or opioid prescribers in Australia and British Columbia (2011) .....	148
<b>Table 5.1</b> Opioids of interest.....	161
<b>Table 5.2</b> Variables requested regarding cohort demographics .....	164
<b>Table 5.3</b> Australian Pharmaceutical Benefits Scheme data on opioid dispensing (and other drug dispensing) history.....	165
<b>Table 6.1</b> Summary and description of all measures and time period of assessment .....	192
<b>Table 6.2</b> Cohort sociodemographics and clinical profile .....	197
<b>Table 6.3A</b> Number of unique opioid prescribers stratified by dispensings, persons and individual factors.....	202

<b>Table 6.3B</b> Number of unique opioid dispensing pharmacies stratified by dispensings, persons, and individual factors .....	203
<b>Table 6.3C</b> Total opioid dispensings by dispensings, persons, and individual factors.....	204
<b>Table 6.4</b> Separate zero-truncated negative multivariable binomial regression models to examine factors associated with increasing number of unique opioid prescribers, dispensing pharmacies or dispensings in 12 months.....	205
<b>Supplementary Table 6.1</b> List of all PBS-subsidised opioid analgesics and Anatomical Therapeutic Chemical code .....	215
<b>Supplementary Table 6.2</b> List of Rx-Risk tool defined medical conditions and Anatomical Therapeutic Chemical codes .....	216
<b>Supplementary Table 6.3</b> Sensitivity analysis results: separate zero-truncated negative binomial regression models to examine factors associated with increasing number of unique opioid prescribers, dispensing pharmacies or dispensings in 12 months .....	218
<b>Table 7.1</b> Relative misclassification for new adult antipsychotic and opioid analgesic users for each look-back period of interest .....	226
<b>Table 8.1.</b> Summary of other routinely collected health datasets available to link to Pharmaceutical Benefits Scheme dispensing data .....	234
<b>Table 8.2.</b> US Drug Enforcement Agency list of features in an ideal prescription drug monitoring program .....	241
<b>Supplementary Material 2.1</b> Detailed search strategies executed in systematic review.....	255
<b>Supplementary Material 2.2</b> 5-item eligibility criteria tool .....	262
<b>Supplementary Material 2.3</b> Data extraction tool for included studies .....	263

<b>Supplementary Material 2.4</b> <i>A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist</i> .....	269
<b>Supplementary Material 2.5</b> <i>Reference list of excluded studies</i> .....	274
<b>Supplementary Material 2.6.</b> <i>Reference list of included studies</i> .....	289
<b>Supplementary Material 2.7.</b> <i>Summary of included studies</i> .....	293
<b>Supplementary Material 2.8</b> <i>The reported extent of prescription drug misuse based on indicators with a defined threshold</i> .....	333
<b>Supplementary Material 2.9</b> <i>The proportion of prescription drugs dispensed to a misuse cohort: determined by a measure of misuse with a defined threshold</i> .....	341

## **List of Figures**

<b>Figure 1.1</b> Opioid consumption for US, Canada and Australia (2002-2014) .....	8
<b>Figure 2.1.</b> Flow chart of systematic review methodology to identify included manuscripts .	63
<b>Figure 2.2</b> Variation in prevalence of prescription drug access and misuse according to thresholds.....	71
<b>Figure 3.1A</b> Number of dispensing episodes for opioid analgesics by medicine in Australia: 1992 – 2012.....	103
<b>Figure 3.1B</b> Benefit paid by the Australian government for opioid analgesics in Australia: 1992 – 2012.....	103
<b>Figure 3.2</b> Number of hospitalisations by opioid poisoning type across Australia: 1998 – 2009. ....	105
<b>Figure 3.3</b> Number of accidental deaths due to illicit drugs and pharmaceutical opioids in Australia: 2002 – 2011 .....	107
<b>Figure 4.1</b> Violin plot distribution of unique number of prescribers by drug class and jurisdiction.....	133
<b>Figure 4.2</b> Cumulative frequency of unique statin or opioid prescribers by age group (2011) .....	137
<b>Supplementary Figure 4.1A</b> Australian cohort inclusion criteria .....	150
<b>Supplementary Figure 4.1B</b> British Columbian cohort inclusion criteria .....	151
<b>Figure 6.1</b> Cohort inclusion criteria.....	190
<b>Figure 6.2</b> Spectrum of opioid access patterns over one year after initiating or reinitiating strong opioid treatment: violin plot with shaded centile bounds.....	199

**Figure 6.3** Relationship between persons at the 90<sup>th</sup> centile or greater for at least one metric .....200

**Figure 8.1** Implementing evidence-based metrics in prescription drug monitoring programs to identify potentially harmful access patterns .....243

## ***List of Abbreviations***

ACT	Australian Capital Territory
AD	Antidepressant
AP	Antiparkinson
ATC	Anatomical Therapeutic Chemical
ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ARIA	Accessibility/Remoteness Index of Australia
AU\$/A\$	Australian dollars
BC	British Columbia
BCE	Before Common Era
BJCP	British Journal of Clinical Pharmacology
BMT	Buprenorphine maintenance treatment
BZD	Benzodiazepine
CI	Confidence interval
CNS	Central nervous system
COD	Cause of death
COMM	Current Opioid Misuse Measure
CREMA	Centre of Research Excellence in Medicines and Ageing
DDD	Defined daily dose
DDD/1000 pop	Defined daily dose per 1000 population
DHS	Australian Government Department of Human Services

DORA	DAPIS online remote access
DSI	Doctor shopping indicator
DSM	American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders
DSQ	Doctor shopping quantity
DUMA	Drug Use Monitoring in Australia
DUSC	Drug Utilisation Sub-Committee
DVA	Australian Government Department of Veterans' Affairs
DZE	Diazepam milligram equivalent
ED	Emergency department
ER	Extended release
ESRI ArcGIS	Geographical information system to present spatial data, create layered maps and perform basic spatial analysis; developed by ESRI
FDA	Food and Drug Administration
GP	General practitioner
HDB	High dosage buprenorphine
HREC	Human Research Ethics Committee
ICD	International Statistical Classification of Diseases and Related Health Problems
ICD-9	International Statistical Classification of Diseases and Related Health Problems, 9 <sup>th</sup> edition
ICD-10-AM	International Statistical Classification of Diseases and related Health Problems, 10 <sup>th</sup> edition – Australian Modification
ICD-CM	International Classification of Diseases – Clinical Modification

IDRS	Illicit Drug Reporting System
INCB	International Narcotics Control Board
IQR	Interquartile range
IR	Immediate release
IRR	Incidence rate ratio
IRSD	Australian Index of Relative Socioeconomic Disadvantage
LA	Long acting
MIMS	Monthly Index of Medical Specialities
MPE(s)	Multiple prescriber episode(s)
MRDD	Maximum recommended daily dose
NCETA	National Centre for Education and Training on Addiction
NCIS	National Coronial Information System
NDARC	National Drug and Alcohol Research Council
NDSHS	National Drug Strategy Household Survey
NHMD	National Hospital Morbidity Database
NHMRC	National Health and Medical Research Council
NHS	National Health Survey
NM	No meaningful result was obtained
NOPS	National Opioid Pharmacotherapy Statistics
NPDMS	National Pharmaceutical Drug Misuse Strategy
NR	Not reported in original manuscript
NSAID	Nonsteroidal anti-inflammatory drug
NSW	New South Wales
OME	Oral morphine equivalent

OMT	Opioid maintenance therapy
Opioid(s)	Opioid analgesic(s)
OR	Odds ratio
ORT	Opioid Risk Tool
OTC	Over-the-counter
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBS	Australian Pharmaceutical Benefits Scheme
PBS10%	Standardised dataset comprised of a random 10% sample of PBS-eligible Australians dispensing history from March 2005; generated by the Australian Government Department of Human Services
PGA	Pharmacy Guild of Australia
PhD	Doctor of Philosophy
PHSREC	Population and Health Services Research Ethics Committee
PDMP	Prescription drug monitoring program
PMP	Prescription monitoring program
POPPY10%	Dataset comprised of a random 10% sample of PBS-eligible Australian adults dispensed a strong prescription opioid
POINT	Pain and Opioids in Treatment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
QOL	Quality of life
RCT	Randomised clinical trial
RM	Relative misclassification

Rx-Risk	Rx-Risk tool is a validated measure to identify the presence of a specific medical condition based on pharmaceutical claims data over one-year
S100 HSDP	Section 100 Highly Specialised Drugs Program
SA	Short acting
SA2	Statistical Level Area 2
SAS	Statistical Analysis Software
SEIFA	Socio-Economic Indexes for Areas (includes a measure of socio-economic disadvantage); developed by the Australian Bureau of Statistics
SF-36	Short Form Health Survey 36-items
SLA	Statistical Local Area
SM	Supplementary material
SOAPP	Screeener and Opioid Assessment for Patients with Pain
Stata	Stata: Data Analysis and Statistical Software
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TGA	Australian Government Department of Health, Therapeutic Goods Administration
UPA	University of Sydney Postgraduate Award
US/USA	United States of America
US\$	United States of America dollars
WHO	World Health Organization

## ***Chapter One: Introduction***

This thesis examines methods of quantifying population prescription drug use and potential misuse in pharmaceutical claims, with a specific interest in prescription opioid analgesics. In this chapter we ♦ provide background information for each research component related to our objective. Specifically, we outline the following issues in relation to prescription opioids: global rates of use; benefits, risks and harms associated with opioid use; and, real world methods of quantifying prescription opioid use in routine clinical care. As the vast majority of research in this field to date is set in North America, this aspect of the chapter is largely US-centric. However, the latter part of the chapter focuses on prescription opioid use and potential misuse in the Australian context and details aspects of the Australian healthcare system to provide the context for our research.

In this thesis we use the term prescription drug(s) to refer to substances prescribed by a doctor to treat a medical condition. The Australian National Medicines Policy uses the term ‘prescribed medicines’ to refer to these substances.<sup>1</sup> Throughout the thesis chapters we use the term ‘prescription drug’ as the majority of our research is published in international journals and this term is frequently used. We use the terms ‘extramedical use’ and ‘misuse’ interchangeably to refer to ‘any use of a prescription opioid or drug outside a doctor’s prescription, not excluding the possibility that the user may have a medically driven reason for using the drug’.<sup>2,3</sup> We also use the term diversion to refer to ‘the unsanctioned supply of

---

♦ The work contained in this thesis was conducted by the PhD candidate in collaboration with PhD supervisors and co-authors listed on the papers arising from each empirical chapter in this thesis.

regulated pharmaceuticals from legal sources to the illicit drug market, or to persons for whom the drug was not intended'.<sup>2,4</sup>

Formatting note: To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. We provide the reference list at the end of this chapter.

## **1.1 Prescription drug use**

Prescription drugs are used to treat, maintain or prevent a medical disease or condition. There are benefits and risks associated with any treatment involving prescription drugs, including side effects and adverse events; doctors must assess this risk-benefit profile at the time of prescribing. The likelihood of adverse outcomes occurring may increase if prescription drugs are taken in larger quantities or a longer time period than medically recommended; or when combined with other prescription or illicit drugs, or alcohol. Although all prescription drugs have side effects, prescription opioids are the most commonly misused drug class.<sup>5</sup> The risks associated with these drugs include overdose, hospitalisation and/or death. Due to the considerable increase in opioid-related harms, prescription opioid misuse is now considered an epidemic in the US.<sup>6</sup> Of concern, there is emerging Australian evidence documenting increases in opioid use and related harms.<sup>7-10</sup> Due to the increasing prominence of opioid risk and harms, coupled with the emerging evidence of increasing opioid use locally, we have chosen to focus on prescription opioids for the majority of our research.

## **1.2 Prescription opioid analgesics**

### *1.2.1 What is an opioid?*

‘Opioid’ is an umbrella term for natural and synthetic drugs derived from or based on opium, which is extracted from the poppy plant *Papaver somniferum*.<sup>11</sup> Prescription opioid analgesics are prescribed most commonly to relieve pain. In this thesis, we refer to these opioids, as prescription opioid analgesic(s), opioid(s), opioid analgesic(s) and prescription opioid(s).

Opioid analgesics are a complex drug class to study. They are the most effective pharmacological pain relievers,<sup>12</sup> but they are also highly addictive and sought for recreational purposes. If a person becomes dependent on opioids, they will require escalating opioid dosages to function and prevent withdrawal symptoms. Over the past two decades, opioid use and related harms have escalated to alarming levels. It has been argued that policymakers, legislators, the medical community and patients should unite to reduce opioid misuse without restricting opioid access or jeopardising pain treatment.<sup>13</sup>

### *1.2.2 Brief history of opium to opioid use*

Opium has been used for millennia. Since 4000 Before Common Era (BCE), people have used opium to provide pain relief and induce euphoria.<sup>11</sup> From 2000 BCE the Egyptians recorded the healing properties of opium in their medical text, *Ebers papyrus*,<sup>5,11,12</sup> and used opium-soaked sponges to facilitate surgery.<sup>14</sup>

Morphine, codeine and diamorphine were the first prescription opioids synthesised for medical purposes in approximately 1804, 1832 and 1874 respectively.<sup>11,14</sup> Opioids were prescribed to treat pain, alcohol dependence, menstrual cramps, menopausal disorders, opium dependence, and cough (suppression).<sup>11,14</sup> However, opioid dependence became a major public health concern at this time. Due to various US legislative decisions, doctors were legally prosecuted if they prescribed opioids for any substance dependence.<sup>11,14</sup> Consequently, doctors largely stopped prescribing opioids for any medical condition for fear of legal ramifications.

In the second half of the 20<sup>th</sup> century clinicians fought to destigmatise opioid treatment. In the 1960s, the Hospice Movement in Western countries fought and won the right to prescribe opioids for symptom management of cancer pain.<sup>15</sup> The medical indication for opioids was extended to include palliative care and symptom management for other illnesses including human immunodeficiency virus.<sup>15</sup> In the 1990s, the indication was again expanded to include management of all noncancer pain including chronic pain.<sup>15,16</sup> Today, in many jurisdictions including US, Canada and Australia, the medical indications for opioid treatment include: episodic, chronic, cancer and noncancer pain, including palliative care and opiate maintenance therapy. Across these jurisdictions, as the medical indications for prescribed opioid widened, opioid use and related harms increased.

Although the medical indications for opioids include both pain and opioid dependence, in this thesis we focus exclusively on opioids prescribed for pain. Our overarching aim is to quantify population prescription drug and opioid use in national pharmaceutical claims. Our Australian pharmaceutical claims data do not record the details of opioids dispensed for the indication of opiate maintenance therapy.

#### *1.2.4 Pain*

Pain is *“an unpleasant physical sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”*<sup>17</sup> and *“pain is always subjective”*.<sup>17</sup> These definitions highlight the primary challenges of treating pain, it is subjective and intangible; there is a lack of any objective medical tests to quantify pain intensity or even its existence. Consequently, every prescription for opioids to provide pain

relief involves uncertainty on the behalf of prescribers, as they will never know whether their patients actually experience pain.

Opioids are used to treat both acute and chronic pain. Acute pain is defined as *'the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus'*<sup>18</sup> and generally resolves when the injury heals. The definition of chronic pain varies in the literature; however, a common definition is pain persisting for  $\geq 3$  consecutive months.<sup>19</sup>

### *1.2.5 Prevalence and burden of pain*

Pain is a common medical complaint and contributes to a significant societal economic burden. Globally, approximately 1 in 5 adults suffer from pain and another 1 in 10 adults are diagnosed with chronic pain annually.<sup>20</sup> According to the US Medical Expenditure Panel Survey, in 2008 approximately 100 million persons (33% of the US population) experienced chronic pain.<sup>21</sup> In 2010 in the US, the total cost of pain was US\$635 billion.<sup>21</sup> The annual cost of pain is considerably higher than other common chronic illnesses such as heart disease (US\$309 billion), cancer (US\$243 billion), and diabetes (US\$188 billion).<sup>22</sup> Coinciding with the increase in reported pain prevalence, global opioid consumption is also increasing.

### *1.2.6 Global opioid consumption*

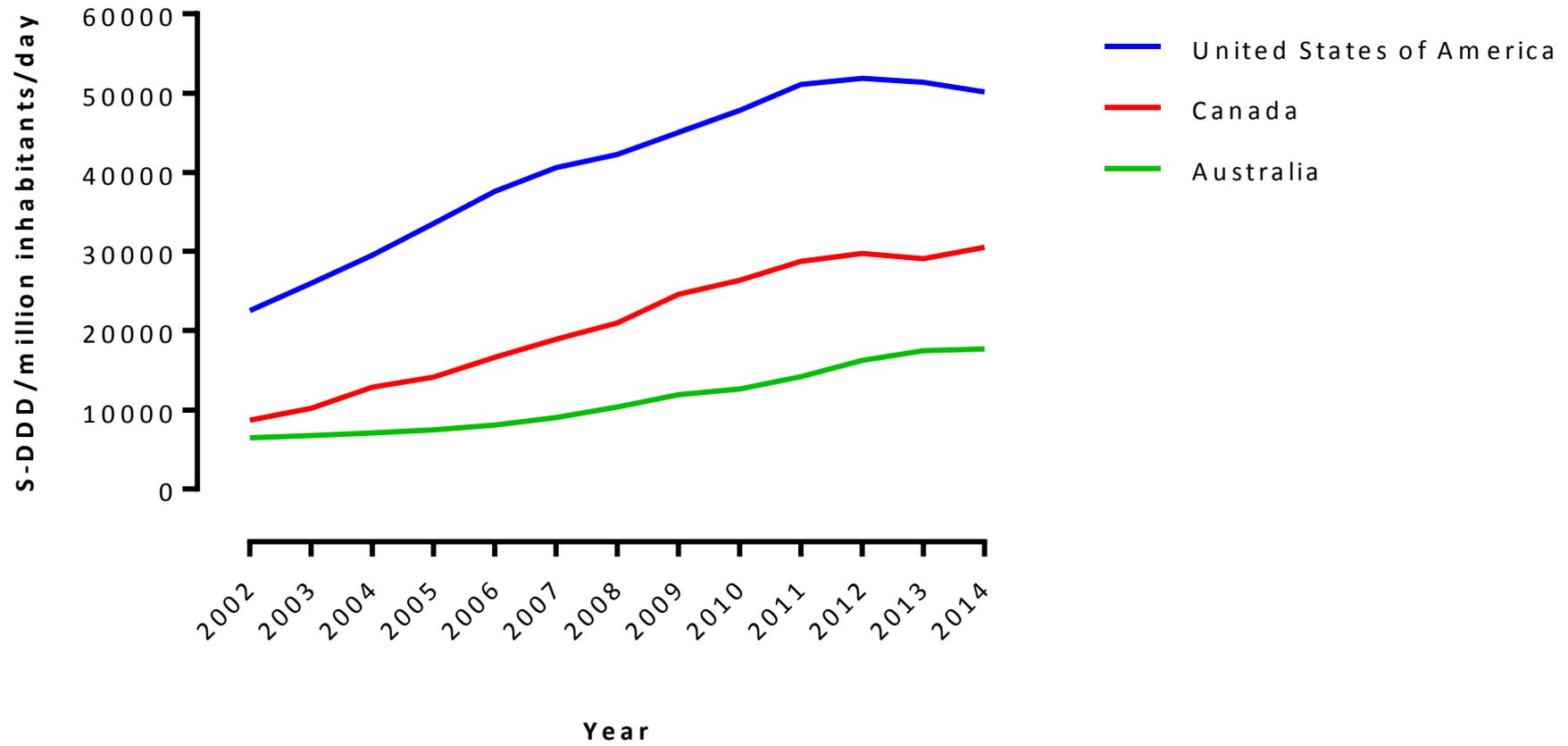
Global opioid consumption is increasing rapidly.<sup>23</sup> The International Narcotics Control Board (INCB) reports annual opioid consumption by jurisdiction. The INCB was established by the Single Convention on Narcotic Drugs in 1961 and merged two bodies: the Permanent Central Narcotics Board, created by the 1925 International Opium Convention; and the Drug Supervisory Body, created by the 1931 Convention for Limiting the Manufacture and

Regulating the Distribution of Narcotic Drugs.<sup>24</sup> The goal of the INCB is to monitor and support governments' compliance with international drug control treaties.

Since 2002, the INCB reports annual total opioid consumption by country according to defined daily dose for statistical purposes per one million inhabitants per day (S-DDD/million inhabitants/day).<sup>25</sup> This methodology was derived from the World Health Organization's (WHO's) defined daily dose (DDD) method which aims to standardise the reporting of prescription drug consumption to facilitate temporal and cross-jurisdictional comparisons. WHO calculates the DDD per drug formulation; one DDD is the average amount of drug required to treat one adult for one day for the main indication of the drug.<sup>26</sup> Importantly, the DDD for opioid analgesics were first developed for the indication of cancer pain, which requires higher doses than the treatment of noncancer pain. Consequently, opioid consumption as reported by DDD generally underestimates total population opioid use.

The INCB reported Australia's 2014 opioid consumption was 17 667 S-DDD/million inhabitants/day which ranked Australia eighth behind US, Canada, Germany, Denmark, Belgium, Austria and Switzerland respectively.<sup>24</sup> Figure 1.1 demonstrates the considerable differences in opioid use between US, Canada and Australia.

Figure 1.1 Opioid consumption for US, Canada and Australia (2002-2014)



Globally, prescription opioid use is more prevalent in specific geographical locations. For example, between 2010 and 2012, North America, Western Europe and Oceania (including Australia) consumed 92% of the global morphine supply, despite accounting for only 17% of the global population.<sup>27</sup> This increase in opioid consumption is largely driven by noncancer pain treatment.<sup>28-30</sup>

Paradoxically, despite the considerable increase in global opioid consumption, the prevalence and economic burden of pain has continued to increase, particularly in the US.

### ***1.3 Prescription opioid treatment guidelines***

Pain guidelines are an important clinical instrument for prescribers as they are based on clinical evidence regarding efficacy and safety of opioids as well as best practice guidelines. In addition, they recommend particular treatments for specific pain conditions. Arguably, one of the contributory factors to the increase in opioid use is the majority of pain guidelines recommending opioids as first-line treatment for all pain relief, regardless of the underlying condition.

Pain guidelines are available to standardise and improve the quality of pain treatment and provide guidance to clinicians prescribing opioids for pain relief.<sup>31</sup> In an effort to educate and guide practitioners, a plethora of pain guidelines are available for specific and general pain conditions.

One of the most commonly cited pain guidelines are the WHO cancer pain ladder for adults.<sup>32</sup> This approach is the basis for opioid treatment for cancer and noncancer pain in

adults. These guidelines recommend three steps to treat pain.<sup>32</sup> The first step is a non-opioid analgesic (e.g. aspirin or paracetamol), if pain persists, then a mild opioid is recommended to treat mild to moderate pain (e.g. codeine). If pain continues then a strong opioid to treat moderate to severe pain (e.g. morphine) may be prescribed. From a public health perspective, the strengths of the WHO step approach are to match the strength of the opioid to pain intensity. It recommends strong opioid use for patients with moderate pain that is unresponsive to weaker opioids and who have multiple interactions with their doctor. This approach may reduce the amount of strong opioids obtained for extramedical purposes. However, from a patient perspective, this strategy may also prolong the experience of severe pain by having to trial, and fail, weaker opioids.

To reduce the incidence of opioid dependence, pain guidelines also suggest doctors assess each patient's suitability for opioid treatment based on their pain condition, medical history, physical tests and risk of substance abuse, misuse or dependence.<sup>33</sup>

Although opioids are consistently recommended in pain guidelines for pain relief for all conditions, the evidence demonstrating the benefits of opioids is weak, particularly long term opioid use for noncancer chronic pain. In the next section we present this evidence as well as the overwhelming research documenting the risks and harms associated with opioid use.

#### ***1.4 Prescription opioids: benefits and risks***

There is copious literature examining the benefits and risks associated with prescription opioids. In this section, we report these outcomes for all opioids as a drug class, meaning we

do not report differences based on a specific opioid, formulation or route of administration. Further, we do not report on opioid treatment for specific pain conditions. In this section we focus on evidence provided by Cochrane reviews, meta-analyses, systematic reviews and draw on other reviews and observational studies where the evidence is weak or lacking.

#### *1.4.1 Benefits of prescription opioid treatment*

Meta-analyses and systematic reviews report prescription opioids provide a 30-63% reduction in cancer and non-cancer pain.<sup>34-38</sup> One systematic review demonstrated seven out of 18 studies found opioid treatment accounted for at least a 50% pain reduction over at least 6 months.<sup>35</sup> A Cochrane review and systematic review investigating long-term opioid treatment ( $\geq 6$  months) for chronic noncancer pain found persons experienced pain relief (quantified as a standardised mean reduction of 1.5 to 7.5 points in pain score).<sup>35,36</sup> The variation in reported pain reduction may be due to the heterogeneity in methods quantifying pain. Evidence surrounding the efficacy of opioid treatment in the longer term is lacking.<sup>5</sup> For example, the Cochrane review included 26 studies with a median of 13 months follow up (range: 6-48 months). Of note, 11 studies (42%) had an observation period of  $\leq 12$  months and eight studies (31%) had an observation period of at least 3 years. These observation periods are relatively short considering persons may use opioids chronically for several years.

##### *1.4.1.1 Functioning and quality of life*

The evidence concerning the impact of opioid treatment on functioning and quality of life (QOL) are weak and conflicting. A Cochrane review investigating QOL and functional status after at least 6 months of opioid treatment noted there was insufficient evidence to make

any conclusions.<sup>36</sup> A systematic review focusing on older persons found short term opioid treatment was associated with better physical functioning but poorer mental health functioning.<sup>38</sup>

Due to the minimal clinical evidence available investigating the long term outcomes of opioid treatment, we examined findings from observational studies. Two Danish studies found opioid use was associated with negative long term outcomes in chronic pain patients (persons experiencing pain for at least 6 months).<sup>39,40</sup> One study compared QOL and functional capacity by stratifying a chronic pain population by opioid use. After controlling for pain level and other factors, opioid use was significantly associated with higher levels of reporting moderate to very severe pain; poor self-rated health; unemployment; higher use of healthcare services; and lower QOL, compared to persons who did not use opioids.<sup>39</sup> The other Danish study examined health outcomes in chronic pain patients 10 years post treatment at a pain centre and found opioid users had lower health-related QOL compared to persons who did not use opioids.<sup>40</sup>

The evidence demonstrating the benefits of opioid treatment is weak, particularly regarding prolonged use and outcomes. In fact, some evidence demonstrates prolonged opioid use may be harmful, particularly in the long term. The majority of evidence originates from randomised clinical trials (RCTs) which, by their nature, focus on the safety and efficacy of opioids over a short time period, rather than investigate long term outcomes including analgesia, QOL and functioning. Also, RCTs examining opioid treatment typically have small sample sizes, high dropout rates, and compare safety and efficacy between opioids rather than a non-pharmacological treatment.<sup>41-43</sup> Furthermore, these studies predominantly focus

on noncancer pain populations;<sup>44</sup> routinely exclude individuals with a history of alcohol or drug dependence;<sup>45</sup> and are predominantly funded by pharmaceutical companies,<sup>5,37</sup> all of these study factors introduce varying degrees of bias. Observational studies have the capability to examine long term outcomes of opioid treatment and complement the findings of RCTs by addressing these methodological shortcomings.

#### *1.4.2 Risks of prescription opioid treatment*

##### *1.4.2.1 Ineffective analgesia and side effects*

Two systematic reviews found 6-12% of persons using opioids do not experience pain relief.<sup>35,37</sup> A multitude of review articles demonstrate up to 80% of persons on opioid treatment experience side effects or adverse events.<sup>34-37,43,46-49</sup> Common side effects include dry mouth, gastrointestinal effects (including constipation), nausea/vomiting, headache, fatigue, sedation, clouded mentation, dizziness and urinary complications.<sup>50</sup> A systematic review found long-term opioid treatment is associated with increased risk of overdose, opioid abuse, fractures, myocardial infarction, and sexual dysfunction.<sup>51</sup>

##### *1.4.2.2 Opioid tolerance and dependence*

Repeated and prolonged exposure to opioid analgesics result in tolerance, which reduces the analgesic efficacy of the drug and is compensated by increasing the opioid dose.<sup>52</sup>

Multiple observational studies have demonstrated high opioid dose is associated with an increased risk of opioid-related harm including overdose and death; as dose increases so does the risk of harm.<sup>53-55</sup> In some cases dose escalation may lead to a patient developing iatrogenic dependence, i.e. when a patient becomes opioid dependent during opioid

treatment for pain. The prevalence of iatrogenic dependence is unknown due to a paucity of research examining this issue.<sup>56</sup>

Estimates of opioid abuse or dependence (hereafter referred to as dependence) vary across studies. RCTs and clinical studies report only 0.04-0.4% of patients develop opioid dependence.<sup>35,36</sup> However, due to the short time period of assessment, pre-market clinical trials may not have the capability to identify dependence, as this generally emerges over a longer time period than the duration of a trial.<sup>45</sup> Studies based on real-world data report the rate of opioid dependence ranges between 0.6-14%.<sup>35-37,57,58</sup> Review articles report considerably higher rates of opioid dependence, ranging between 0-50% in noncancer patients<sup>57,59-61</sup> and 0-7.7% in cancer patients treated for pain.<sup>59,61</sup> The variation in reported rates may be due to methodological heterogeneity in the measures quantifying prescription opioid dependence. Chapter Two of this thesis provides a more detailed examination of how prescription drug misuse, including opioid misuse, is quantified in observational studies using pharmaceutical claims data.

### ***1.5 Prescription opioid-related harms***

While opioids are the most effective pharmacological option to treat pain, several North American ecological studies demonstrate an increase in opioid use is associated with an increase in opioid-related harms.<sup>6,62-65</sup> In summary, since the 1990s there have been considerable increases in recreational prescription opioid use and related-harms including poisonings, emergency department presentations, hospitalisations and deaths. Recent evidence suggests these harms are plateauing;<sup>66</sup> however, these harms still represent a significant public health concern.

### *1.5.1 Recreational opioid use*

In 2014, the US National Survey on Drug Use and Health found 6.5 million Americans reported non-medical use of a prescription drug (including opioids, sedatives, stimulants and tranquilisers); representing 2.5% of the US population aged  $\geq 12$  years.<sup>67</sup> This figure is largely driven by opioids, as two-thirds of this population (4.3 million persons) misused prescription opioids.<sup>67</sup>

### *1.5.2 Opioid harms*

Prescription opioids are depressants, they slow down the central nervous system including respiration and heart rate.<sup>68</sup> An opioid overdose or poisoning occurs when the body cannot adequately breakdown the quantity of opioids ingested, consequently, normal functions, such as breathing or heart rate, may decrease to dangerous levels or stop completely. Depending on the amount of opioids consumed and access to medical treatment, an opioid overdose may result in an emergency department (ED) presentation, hospitalisation and/or death.<sup>68</sup> The risk of opioid harm increases if opioids are taken in conjunction with other substances including alcohol, illicit drugs or prescription drugs such as benzodiazepines.<sup>69</sup>

Multiple studies have demonstrated increases in opioid poisonings in recent years.<sup>70-72</sup>

Between 1999 and 2006, opioid poisonings in the US increased 3.5 fold (4 000 to 13 800 poisonings annually).<sup>73</sup> These harms also represent a significant economic burden. In 2009, the estimated cost of opioid poisonings was US\$20.4 billion.<sup>73</sup> The majority of these costs are work-related including lost future earnings due to mortality (US\$18.2 billion) and absenteeism (US\$335 million). Direct medical costs totalled US\$2.2 billion; inpatient costs

accounted for US\$1.3 billion and ED presentations accounted for the remaining US\$800 million.<sup>73</sup>

Multiple studies have demonstrated increases in opioid-related ED visits or hospitalisations.<sup>74-77</sup> Between 1993 and 2010, the rate of ED presentations for opioid toxicity in the US increased almost 3.5 fold, from 19 to 63 per 100 000 population.<sup>75</sup> In 2010, prescription opioids accounted for 41% of the 731 000 ED presentations for overdoses.<sup>75</sup>

Rates of hospitalisation due to opioid dependence increased 1.7-fold between 2002 and 2012 and cost US\$15 billion.<sup>76</sup> In 2012 alone, these hospitalisations cost US\$700 million.<sup>76</sup> In 2008, the total cost of ED/hospital visits for opioid-dependent persons in the US was US\$9.5 billion.<sup>78</sup>

Multiple studies have documented the increase in opioid-deaths.<sup>69,79-86</sup> In 2008, there were approximately 36 450 drug overdose deaths; equating to one death every 14.5 minutes.<sup>86</sup> In 2008, there were 20 044 prescription drug overdose deaths, of which, prescription opioids accounted for 14 800 (74%) deaths.<sup>86</sup> In the US between 2000 and 2014, the rates of opioid-related deaths increased 200%; with a 14% increase between 2013 and 2014 alone (7.3 to 9.0/100 000 population).<sup>79</sup>

### *1.5.3 Economic impact of opioid misuse*

As well as the increase in opioid-related harms, prescription opioid misuse also represents a significant economic burden to the community. At an individual level, several studies have

demonstrated that opioid-dependent persons have 1.4 to 8.7 times higher healthcare costs than their non-dependent counterparts.<sup>87-91</sup>

At a societal level, the cost of opioid misuse and dependence increased 6.5 fold between 2001 and 2007; costing up to US\$55.7 billion in 2007 alone.<sup>92-94</sup> Workplace (US\$25.5 billion, 46%) and healthcare (US\$25 billion, 45%) costs together account for over 90% of total costs; the criminal justice system accounts for the remainder (US\$5.1 billion).<sup>91</sup> As opioid use has continued to increase over the past 10 years, these costs are also likely to have increased.

Prescription opioids are a complex and controversial drug class. The WHO lists opioids as an essential medicine, meaning opioids should be available at all times in adequate amounts, with assured quality and priced affordably for the individual and community.<sup>95</sup> However, there is weak evidence demonstrating opioids efficacy to treat chronic pain, particularly exploring long term outcomes of opioid use. In this section we highlighted the considerable increases in US opioid-related harms. Similar trends have emerged from other jurisdictions including Canada,<sup>64,96,97</sup> Great Britain<sup>98</sup> and Australia.<sup>8-10,99</sup> Opioid misuse and dependence also represent a significant economic burden, both at individual and societal levels. Despite this evidence, there is relatively limited scholarship examining real world opioid use and access patterns.

### ***1.6 Real world methods of quantifying prescription opioid misuse***

In this section we highlight the major challenges in quantifying prescription opioid misuse.

As opioid-related harms have increased considerably it is believed that rates of opioid misuse are also increasing. However, there is no consensus on the definition of misuse.<sup>2,100-</sup>

<sup>108</sup> In this section we examine the strengths and weaknesses of the dominant methodologies to quantify misuse in the real world including structured clinical interviews, questionnaires, medical chart review and routinely collected data.

### *1.6.1 Structured clinical interviews*

The main goal of a structured clinical interview is to determine if a person meets the diagnostic criteria of opioid misuse or dependence. Two internationally recognised clinical tools to diagnose opioid misuse or dependence are the International Statistical Classification of Diseases and Related Health Problems (ICD)<sup>109</sup> and the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM).<sup>110</sup> These clinical tools may also be adapted for research purposes to quantify the extent of dependence without any clinical implications. Structured clinical interviews are generally conducted by trained clinicians such as a psychiatrist. The interview is usually based on a set of pre-determined questions, regarding another individual's opioid use and the impact of opioids on their life.

Two Australian studies compared the prevalence of opioid misuse quantified by the ICD (edition 10 and draft of edition 11), the DSM (editions 4 and 5) and "addiction" as defined by Pain Medicine as including at least one of the following symptoms: impaired control over drug use, compulsive use, continued use despite harm and cravings. Lifetime rates of opioid-misuse were quite similar across all measures (9-10%), however, the extent over 12-months varied from 18-24%.<sup>111,112</sup> These differences are due to the unique diagnostic criteria used in each measure.

From a research perspective, these interviews are time consuming, not necessarily representative of the general population, rely on a patient's recall and have inherent biases including social desirability and truth bias. For example, persons may under-report opioid use as it may be more socially desirable and they may fear negative judgement from the interviewer.

### *1.6.2 Questionnaires*

Questionnaires may be used to characterise past opioid access and determine the risk of future extramedical drug seeking behaviour; in this section we focus on the latter.

Questionnaires may form part of routine patient intake for pain clinics<sup>113</sup> and are usually self-report. There are a multitude of validated measures predicting future misuse including Screener and Opioid Assessment for Patients with Pain (SOAPP);<sup>114</sup> Opioid Risk Tool (ORT)<sup>115</sup> and Current Opioid Misuse Measure (COMM).<sup>116</sup>

Several studies have compared the psychometric properties of these measures to determine their validity in different patient populations.<sup>108,113,117,118</sup> The results of these studies are mixed. One review found the combination of a clinical interview with the SOAPP questionnaire was the most sensitive tool to predict opioid misuse followed by clinical interview or SOAPP alone, respectively.<sup>113</sup> Another review found that high scores on the SOAPP, COMM and ORT were associated with increased likelihood of future extramedical drug seeking behaviour, and low scores on each of these measures was associated with a decreased risk of such behaviour.<sup>108</sup> However, the evidence regarding the validity of these questionnaires are weak.<sup>108</sup>

From a research perspective, the strengths of patient self-report questionnaires include a relatively short time period to complete the measure and larger sample sizes than RCTs or studies using structured clinical interviews.<sup>119</sup> Questionnaires have similar weaknesses to interviews including samples that are unrepresentative of the general population. For example, males may be overrepresented and minority groups underrepresented.<sup>118</sup> Questionnaires also have inherent truth, recall and social desirability bias.<sup>113,120</sup> Further, there may be a non-response bias, meaning the generalisability of the results is limited due to large numbers of persons in the population of interest not completing the questionnaire.<sup>119</sup>

### *1.6.3 Medical chart review*

A chart review involves examining patient medical records from a healthcare setting such as a hospital or general medical practice. In pharmacoepidemiological studies, a researcher may audit these health records to examine prescription drug use and/or clinician prescribing patterns.

Multiple studies have used a chart review to examine important clinical questions such as opioid initiation, switching, tolerability, effectiveness, prevalence of potential misuse and/or substances involved in a prescription drug-related death.<sup>121-124</sup>

The strength of these data is the wealth of patient information available including over-the-counter drug use, comorbid medical conditions, body mass index, family history, smoking status, alcohol use and illicit substance use.<sup>125</sup> The limitations of chart reviews include being largely descriptive in nature, as outcome data is only included if a patient discloses this

information and the doctor records it. Based on the studies above, they have relatively small sample (range: 61-617 people); consequently, results may be biased to persons seeking treatment for the condition of interest, which may not be representative of the entire population. Furthermore, the information may vary in completeness due to a patient receiving treatment from multiple facilities and the quality and legibility of doctor's notes.<sup>121</sup>

#### *1.6.4 Routinely collected data*

Routinely collected data are information collected for a purpose other than research. These data are collected by governments, healthcare providers and insurers.<sup>126</sup> In section '1.5 *Prescription opioid-related harms*' we document the considerable increases in opioid-related harms; the majority of these findings were based on routinely collected data, particularly those examining trends of opioid-related ED visits, hospitalisations and deaths.

In this section we focus on pharmaceutical claims that record real world prescription drug dispensings, which provides researchers with the opportunity to examine whole-of-population patterns of opioid use. Pharmacoepidemiological studies perform an important role in examining drug safety and effectiveness in the real world.<sup>121,127</sup> As pharmaceutical claims are based on community access patterns, studies generally have large sample sizes which provides the opportunity to detect rare or uncommon adverse events, examine drug safety and patterns of use.<sup>128,129</sup> Researchers can assess these factors in diverse populations who are not typically represented in RCTs including the elderly, pregnant women and children.<sup>120,127,128,130</sup> This method can provide insights into clinical questions quicker and at a lower cost than other study designs, including RCTs.<sup>129,131-133</sup> Generally, researchers are able to access these data due to privacy legislation including a section concerning waiver of

consent. Consequently, studies are not typically prone to selection bias as per other data sources that require informed consent.<sup>129</sup>

Internationally, pharmaceutical claims have been used extensively to examine prescription opioid use;<sup>7,29,134-138</sup> evaluate new opioid access policies;<sup>55,63,139,140</sup> quantify potential misuse,<sup>141-144</sup> and examine adherence to pain guidelines.<sup>145</sup> Several studies have linked pharmaceutical claims with other electronic health outcome datasets to examine the association between opioid use and harms including overdose and death.<sup>54,54,146-149</sup>

Perhaps the most significant limitation to pharmacoepidemiological research using pharmaceutical claims is it is a relatively new field of study, said to be in its adolescence,<sup>128</sup> therefore its methods require critical analysis. This is particularly true for assessing methods quantifying prescription drug misuse in pharmaceutical claims, as there are no validated definitions of misuse and limited consensus on the behaviour that constitutes extramedical use. Pharmaceutical data generally contain limited clinical information, including no indication of diagnoses; confounders including smoking or alcohol use; or, severity of illness.<sup>120,126,127,129,130,132</sup> Finally, given the large sample sizes, findings are often considered statistically significant so it is important to determine the clinical relevance of all results.

Despite these limitations, pharmaceutical claims are, arguably, the only Australian data available to examine whole-of-population, real world trends in prescription drug use and access patterns. Furthermore, despite the availability of these data and Australia's universal healthcare system, there has been relatively limited research focusing on opioids in pharmaceutical claims. In the next section we focus on the Australian context, specifically,

we document the prevalence of chronic pain, the prevalence of extramedical prescription drug use, and summarise aspects of the Australian healthcare system, focusing on the Australian Pharmaceutical Benefits Scheme, and research examining opioid use and related harms using pharmaceutical claims.

## **1.7 Australia**

### *1.7.1 Pain: prevalence and economic burden*

In Australia in 2001, 17% of males and 20% of females reported chronic pain (experienced pain every day for 3 months in the preceding 6-month period).<sup>19</sup> Prevalence increased with age; at the peak, over one-quarter of Australian males aged 65-69 years and almost one-third of Australian females aged 80-84 years reported chronic pain.<sup>19</sup>

In 2007/2008, the Australian Bureau of Statistics National Health Survey (NHS) quantified the extent of bodily pain in Australia. The NHS found 67% of Australian adults (11.1 million persons) reported experiencing bodily pain in the preceding 4 weeks.<sup>150</sup> Between 1995 and 2007, rates of bodily pain increased from 57% to 68%, respectively, and severe/very severe pain increased from 7% to 10%.<sup>150</sup> In 2007, the cost of chronic pain in Australia was AU\$34.3 billion, equating to AU\$11 000 per person with chronic pain.<sup>151</sup> Specifically, productivity costs (\$11.7 billion; 34%) and the burden of disease (\$11.5 billion; 34%) account for 68% of costs followed by the burden of the health care system (\$7 billion; 20%) and informal care (\$1.3 billion; 0.7%).<sup>151</sup> Due to Australia's ageing population, the proportions of persons experiencing chronic pain and economic burden have likely increased over the past decade.

### *1.7.2 Rates of non-medical prescription drug use*

National Australian surveys report increasing rates of extramedical prescription drug use. Lifetime rates of non-medical use for any prescription drug range from 4.7-11.4%;<sup>152,153</sup> in the 12-months prior to survey completion the rate ranged from 4.2-5.1%.<sup>153-155</sup> Not surprisingly, opioids are the drug class most frequently associated with non-medical use;<sup>153</sup> 3.3% of Australians (approximately 600 000 persons) used opioids for an extramedical purpose over 12 months.<sup>153</sup>

### *1.7.3 Australian healthcare system*

For all studies in this thesis, we analyse Australian Pharmaceutical Benefits Scheme (PBS) data, which is a national pharmaceutical claims dataset. In the remainder of this section, we detail the Australian healthcare system as it relates to our work and data collections that result from interactions with the system.

Medicare is a publically funded universal healthcare system operating in Australia. It was established as Medibank in 1975 and renamed Medicare in 1984.<sup>156</sup> This universal healthcare system entitles all Australian citizens and permanent residents to free or subsidised healthcare including prescription drugs.

### *1.7.4 Australian Pharmaceutical Benefits Scheme (PBS)*

The PBS is a national system that subsidises the cost of a wide range of prescription drugs and provides access to necessary and cost-effective drugs. The PBS was first established in 1948 and provided all drugs free to pensioners and 139 drugs considered to be 'life-saving and disease preventing' free for the community.<sup>157</sup> As of December 2009, the PBS covers

874 drug substances (generic drugs), available in 2 168 formulations/strengths, and marketed as 3 949 products.<sup>152</sup>

The Australian Government Department of Human Services (DHS) are the data custodians of PBS data. These data are restricted to PBS-listed drugs dispensed for a PBS-listed indication where the Australian government provides reimbursement.

#### 1.7.4.1 The process of the Pharmaceutical Benefits Scheme listing a prescription drug on the formulary

To be listed on the PBS, a drug must be assessed and approved by multiple agencies and committees.

The Australian Government Department of Health, Therapeutic Goods Administration (TGA) approves the drug for marketing in Australia based on its clinical efficacy and safety compared to other treatments for the same medical indication.<sup>162</sup> This decision is based on submissions from the drug sponsor who may subsequently apply for PBS-subsidy.

The Pharmaceutical Benefits Advisory Committee (PBAC) evaluate the drug for public subsidy. The PBAC assesses the efficacy, safety and cost-effectiveness of the drug compared to existing treatments for the same indication, as well as the overall cost to the Australian Government.<sup>163</sup> When a drug is PBS-subsidised, it increases community access to the drug and a record is created when it is dispensed. If a drug is not PBS-subsidised but approved by the TGA, it is available for prescription in Australia, however, a patient must pay the full cost of the drug and no dispensing records are collected in PBS claims.

All PBS-listed prescription drugs are assigned a PBS-item code which denotes the prescription drug, strength, formulation and quantity. The PBS-item codes may be mapped to the WHO's Collaborating Centre for Drug Statistics Methodology, Anatomical Therapeutic Chemical (ATC) classification system.<sup>160</sup> According to the ATC methodology, the active substance in all prescription drugs are categorised based on the organ or system on which they act and their therapeutic, pharmacological and chemical properties. The ATC code for opioid analgesics to provide pain relief is N02A. In this thesis we include the PBS-listed opioids: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, tapentadol and tramadol. However, tapentadol is excluded from the majority of our analyses as it was PBS-listed in 2014; after the observation period of our studies.

#### 1.7.4.2 Australian Pharmaceutical Benefit Scheme patient beneficiary categories

The PBS defines two beneficiary levels: concessional and general. Concessional beneficiaries account for approximately 25% of the PBS-eligible Australian population;<sup>161</sup> but in 2014 they obtained almost three-quarters of the 289 million drug dispensings in Australia.<sup>159</sup>

The PBS beneficiary category has implications for data collection, for a detailed discussion of this issue please see our practical guide for researchers using the PBS, provided in Appendix G. In short, historically a PBS dispensing record is created only when the Australian government provides reimbursement for a dispensed drug. Consequently, in the PBS data we have complete dispensing history for concessional beneficiaries, as the government provides reimbursement for all their drug dispensings. However, data completeness varies

for general beneficiaries' data by drug and formulation, as the government only provides reimbursement for higher cost drugs.

Concessional beneficiaries receive a government pension (unemployment, disability, sickness, single-parent or aged pension). In January 2016, the concessional beneficiary copayment was AU\$6.20;<sup>162</sup> the copayment generally increases annually on 1 January. All PBS-listed drugs are priced above the concessional beneficiary copayment so they pay a maximum of their copayment per drug dispensing. The PBS also has a family safety net threshold to subsidise prescription drug costs for chronically ill patients. A family includes the patient, partner, children aged <16 years and full-time students aged <25 years.<sup>163</sup> Once a family spends the safety net threshold on prescription drugs, in a calendar year, their copayment reduces. For concessional beneficiaries, the safety net threshold is AU\$372 (as at 1 January 2016), equating to 60 drug dispensings priced at the concessional beneficiary copayment per calendar year.<sup>167</sup> Once the threshold is reached, the patient copayment reduces to zero for all drug dispensings for the remainder of the calendar year as the Australian government completely subsidises the cost of these dispensings.

General beneficiaries do not receive a government pension. The general beneficiary copayment is currently AU\$38.30 (as at 1 January 2016).<sup>162</sup> PBS-listed drugs may be priced either above or below the general beneficiary copayment. The general beneficiary pays either the cost of the drug or their copayment whichever is less. The cost of any PBS-listed dispensed drug contributes to the safety net threshold. The safety net threshold for general beneficiaries is AU\$1475.70 (as at 1 January 2016), equating to at least 39 dispensings priced at their copayment per calendar year.<sup>162</sup> Once this threshold is reached, the family

pays the concessional beneficiary copayment amount (currently AU\$6.20) for all drug dispensings for the remainder of the calendar year.

#### 1.7.4.3 Australian Pharmaceutical Benefits Scheme data sources

Historically, PBS dispensing data are collected from two data sources. Firstly, a PBS dispensing record is created when a PBS-listed drug is dispensed in the community for a PBS-listed indication, and the cost of the drug is higher than the relevant copayment (in 2016, AU\$6.20 for concessional beneficiaries and AU\$38.30 for general beneficiaries). Consequently, PBS records capture all concessional beneficiary drug dispensings, as all PBS-listed drugs are priced above their copayment. These data exclude under-copayment dispensings (for general beneficiaries only) and private prescriptions, i.e. when a medical practitioner prescribes either a drug that is not PBS-listed or a PBS-listed drug for a medical indication for which it is not PBS-listed.

From 1989 the Drug Utilisation Sub-Committee (DUSC) commissioned the Pharmacy Guild of Australia (PGA) to conduct an annual survey (Pharmacy Guild Survey) to estimate the national volume of dispensings for drugs that are not PBS-listed or subsidised, i.e. private prescriptions and under-copayment dispensings. Total drug dispensings information was collected monthly from pharmacies that were members of the PGA. In 2007, the survey included 370 pharmacies across Australia; representing approximately 6% of the 5 450 community pharmacies currently operating across Australia.<sup>164</sup>

However, in 2012 DHS started collecting data for under-copayment drug dispensings and the Pharmacy Guild Survey ceased. Now, DHS captures dispensings for all concessional and

general beneficiaries, regardless of the drug cost, but no private prescription data. Of note, none of the PBS data examined in this thesis includes under-copayment dispensings. Therefore, we restricted all analyses in this thesis to concessional beneficiaries to ensure complete capture of all drug dispensings for our cohort.

#### 1.7.4.4 Limitations of Australian Pharmaceutical Benefits Scheme data

There are several limitations regarding PBS data. Prior to 2012, PBS data did not collect any information regarding private prescriptions, under-copayment dispensings or drugs that are not PBS-listed. PBS data does not include dispensings for drugs dispensed from public hospitals located in New South Wales or the Australian Capital Territory. In the other six Australian jurisdictions, the Public Hospital Pharmaceutical Reforms allows participating hospitals to provide discharging inpatients and outpatients with PBS-subsidised drugs,<sup>165</sup> which are included in PBS data collections.

In Australia, methadone and buprenorphine are PBS-listed for the indications of pain and opioid dependence. Opioids dispensed for opiate maintenance therapy are classified under the Section 100 Highly Specialised Drugs Program (S100 HSDP) which are run by each individual Australian State or Territory. As the S100 HSDP is not a national scheme, no dispensing records for opioids dispensed for opiate dependence are collected in PBS data. Consequently, these dispensings are not included in any data analysed in this thesis.

The Australian government do not reimburse over-the-counter (OTC) drugs, consequently they are not captured in PBS data. OTC drugs are outside the scope of this thesis, but a few Australian studies have investigated OTC opioid use based on other data.<sup>166-168</sup>

### *1.7.5 National Pharmaceutical Drug Misuse Strategy*

Prescription drug and opioid misuse are recognised as a national issue which needs to be addressed, particularly in light of the evidence demonstrating the considerable increases in opioid use and harms in the US. In 2011, the National Centre for Education and Training on Addiction (NCETA) published a report outlining the major challenges in quantifying prescription drug misuse in Australia.<sup>169</sup> They stipulate:

*“in order to develop appropriate responses to pharmaceutical misuse problems, it is important to establish current levels and patterns of use and misuse, and the extent and nature of harms.”<sup>169</sup>*

They continue to list other difficulties that prevent accurately quantifying misuse including: a lack of pre-existing monitoring systems to identify and track all prescription drug use in a timely manner at the person-level; inability to track drug use across Australian jurisdictions due to different opioid access policies between States and Territories; and a lack of national information to provide a comprehensive picture of prescription drug use.<sup>169</sup> However, routinely collected data, particularly PBS claims, overcome these perceived challenges. Despite this fact, there is scant Australian research investigating prescription drug misuse in pharmaceutical claims.

### *1.7.6 Australian prescription opioid research using pharmaceutical claims*

A recent systematic review identified all Australian pharmacoepidemiological studies using pharmaceutical claims published since 1987.<sup>170</sup> Over one-third (36%) of the 228 Australian

pharmacoepidemiological studies focused on nervous system drugs. However, only five reviewed studies included opioid analgesics.

Australian studies using routinely collected data demonstrated considerable increases in opioid use between 1986 and 2009<sup>7,171-174</sup> and opioid-related harms between 2000 and 2011.<sup>8-10,99</sup> None of these studies provided a national picture of opioid use and opioid-related harms. Excluding the studies presented in this thesis, only one other Australian study has used person-level PBS data to examine opioid use. They found approximately 25% of elderly patients initiating oxycodone did not follow PBS opioid treatment guidelines,<sup>145</sup> i.e. their prescriber did not trial a non-opioid analgesic prior to initiating strong opioid treatment.

There are large gaps in Australia's understanding of opioid use and potential misuse. In this thesis we will explore the issues identified by the NCETA in quantifying national opioid use, patterns of access and the extent of opioid-related harms, by using routinely collected data, predominantly pharmaceutical claims.

## 1.8 References

1. Australian Government Department of Health. National Medicines Policy Document. 2014; <http://www.health.gov.au/internet/main/publishing.nsf/Content/national-medicines-policy>. Accessed 12 August 2016.
2. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick R. Definitions related to the use of pharmaceutical opioids: extramedical use, diversion, non-adherence and aberrant medication-related behaviours. *Drug Alcohol Rev.* 2011; 30(3): 236-245.
3. Degenhardt L, Larance B, Mathers B, Azim T, Kamarulzaman A, et al. Benefits and risks of pharmaceutical opioids: Essential treatment and diverted medication. A global review of availability, extra-medical use, injection and the association with HIV. *Prepared on behalf of the Reference Group to the United Nations on HIV and Injecting Drug Use. Sydney, University of New South Wales* 2008; [https://www.unodc.org/documents/hiv-aids/publications/Benefits\\_and\\_risks\\_of\\_pharmaceutical\\_opioids.pdf](https://www.unodc.org/documents/hiv-aids/publications/Benefits_and_risks_of_pharmaceutical_opioids.pdf). Accessed 24 July 2016.
4. Inciardi JA, Surratt HL, Kurtz SP, Burke JJ. The diversion of prescription drugs by health care workers in Cincinnati, Ohio. *Subst Use Misuse.* 2006; 41(2): 255-264.
5. Katz N. Opioids: after thousands of years, still getting to know you. *Clin J Pain.* 2007; 23(4): 303-306.
6. Manchikanti L, Helm II S, Fellows B, Janata JW, Pampati V, et al. Opioid epidemic in the United States. *Pain Physician.* 2012; 15(3 Suppl): ES9-38.
7. Leong M, Murnion B, Haber PS. Examination of opioid prescribing in Australia from 1992 to 2007. *Intern Med J.* 2009; 39(10): 676-681.

8. Rintoul AC, Dobbin MD, Drummer OH, Ozanne-Smith J. Increasing deaths involving oxycodone, Victoria, Australia, 2000–09. *Inj Prev.* 2010; 17(4): 254-259.
9. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. *Med J Aust.* 2011; 195(5): 280-284.
10. Roxburgh A, Burns L, Drummer OH, Pilgrim J, Farrell M, et al. Trends in fentanyl prescriptions and fentanyl-related mortality in Australia. *Drug Alcohol Rev.* 2013; 32(3): 269-275.
11. Seppala M, Rose M. *Prescription Painkillers: History, Pharmacology and Treatment.* Minnesota, United States of America: Hazelden; 2010.
12. Duarte DF. Opium and opioids: a brief history. *Rev Bras Anesthesiol.* 2005; 55(1): 135-146.
13. Volkow ND, McLellan TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA.* 2011; 305(13): 1346-1347.
14. Stannard C, Coupe M, Pickering T. *Opioids in non-cancer pain.* OUP Oxford; 2013.
15. Ballantyne JC. Palliative care: not only for the dying: care at the close of life: evidence and experience. *Clin J Pain.* 2012; 28(5): 463.
16. Von Korff MR. Opioids for chronic noncancer pain: as the pendulum swings, who should set prescribing standards for primary care? *Ann Fam Med.* 2012; 10(4): 302-303.
17. Merskey H. The definition of pain. *Eur Psychiatry.* 1991; 6(4): 153-159.
18. Federation of State Medical Boards. Model Guidelines for the Use of Controlled Substances for the Treatment of Pain. FSMB Euless, TX; 1998.
19. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, et al. Chronic pain in Australia: a prevalence study. *Pain.* 2001; 89(2): 127-134.

20. Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health*. 2011; 11(1): 1-5.
21. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012; 13(8): 715-724.
22. National Institutes of Health. National Heart Lung and Blood Institute Factbook Fiscal Year 2008. 2010; <https://www.nhlbi.nih.gov/about/documents/factbook>. Accessed 23 July 2016.
23. Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet*. 2016; 387(10028): 1644-1656.
24. International Narcotics Control Board. Narcotic Drugs - Technical Reports. 2016; [https://www.incb.org/incb/en/narcotic-drugs/Technical\\_Reports/narcotic\\_drugs\\_reports.html](https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/narcotic_drugs_reports.html). Accessed 19 June 2016.
25. International Narcotics Control Board. Definition of S-DDD. 2016; <https://www.incb.org/incb/en/narcotic-drugs/Availability/availability.html>. Accessed 26 June 2016.
26. World Health Organization Collaborating Centre for Drug Statistics Methodology. Defined daily dose: definition and general considerations. 2009, [http://www.whocc.no/ddd/definition\\_and\\_general\\_considera/](http://www.whocc.no/ddd/definition_and_general_considera/). Accessed 23 July 2016.
27. International Narcotics Control Board. Availability of narcotic drugs for medical use. 2016; <https://www.incb.org/incb/en/narcotic-drugs/Availability/availability.html>. Accessed 26 June 2016.

28. Azevedo LF, Costa-Pereira A, Mendonça L, Dias CC, Castro-Lopes JM. A population-based study on chronic pain and the use of opioids in Portugal. *Pain*. 2013; 154(12): 2844-2852.
29. Fredheim OM, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway. *Eur J Pain*. 2010; 14(3): 289-294.
30. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain*. 2014; 18(9): 1343-1351.
31. Trescot AM, Boswell MV, Atluri SL, Hansen HC, Deer TR, et al. Opioid guidelines in the management of chronic non-cancer pain. *Pain Physician*. 2006; 9(1): 1.
32. World Health Organization. WHO's cancer pain ladder for adults. 2016; <http://www.who.int/cancer/palliative/painladder/en/>. Accessed 16 June 2016.
33. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009; 10(2): 113-130.
34. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004; 112(3): 372-380.
35. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage*. 2008; 35(2): 214-228.
36. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev*. 2010; 1(1): CD006605.
37. Papaleontiou M, Henderson Jr CR, Turner BJ, Moore AA, Olkhovskaya Y, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in

- older adults: a systematic review and meta-analysis. *J Am Geriatr Soc.* 2010; 58(7): 1353-1369.
38. Lorenz KA, Lynn J, Dy SM, Shugarman LR, Wilkinson A, et al. Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med.* 2008; 148(2): 147-159.
  39. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain.* 2006; 125(1): 172-179.
  40. Jensen MK, Thomsen AB, Højsted J. 10-year follow-up of chronic non-malignant pain patients: opioid use, health related quality of life and health care utilization. *Eur J Pain.* 2006; 10(5): 423-423.
  41. Millennium Pain Center. Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician.* 2008; 11: S181-S200.
  42. Kissin I. Long-term opioid treatment of chronic nonmalignant pain: unproven efficacy and neglected safety? *J Pain Res.* 2013; 2013(6): 513-529.
  43. Stein C, Reinecke H, Sorgatz H. Opioid use in chronic noncancer pain: guidelines revisited. *Curr Opin Anesthesiol.* 2010; 23(5): 598-601.
  44. Koyyalagunta D, Bruera E, Solanki D, et al. A systematic review of randomized trials on the effectiveness of opioids for cancer pain. *Pain Physician.* 2012; 15(3 Suppl): ES39-58.
  45. Schifano F, Papanti GD, Orsolini L, Corkery JM. The consequences of drug misuse on post-marketing surveillance. *Expert Rev Clin Pharmacol.* 2016; 9(7): 867-871.
  46. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ.* 2006; 174(11): 1589-1594.

47. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther.* 2005; 7(5): R1046.
48. McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain.* 2003; 4(5): 231-256.
49. Manchikanti L, Vallejo R, Manchikanti K, Benyamin RM, Datta S, et AL. Effectiveness of long-term opioid therapy for chronic non-cancer pain. *Pain Physician.* 2011; 14: E133-E156.
50. Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician.* 2011; 14: 91-121.
51. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015; 162(4): 276-286.
52. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med.* 2003; 349(20): 1943-1953.
53. Braden J, Russo J, Fan M, Edlund MJ, Martin BC, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med.* 2010; 170(16): 1425-1432.
54. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med.* 2010; 152(2): 85-92.

55. Gomes T, Juurlink D, Yao Z, Camacho X, Paterson JM, et al. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: a time series analysis. *CMAJ Open*. 2014; 2(4): E256-E261.
56. Hartman H. Risk factors for iatrogenic opioid dependence: an Australian perspective. *Australian Medical Student Journal*. 2015: 23.
57. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug - related behaviors? A structured evidence - based review. *Pain Med*. 2008; 9(4): 444-459.
58. Bannwarth B. Risk-benefit assessment of opioids in chronic noncancer pain. *Drug Saf*. 1999; 21(4): 283-296.
59. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain*. 2007; 11(5): 490-518.
60. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015; 156(4): 569-576.
61. Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. *Addiction*. 2013; 108(4): 688-698.
62. Bohnert AS, Ilgen MA, Trafton JA, Kerns RD, Eisenberg A, et al. Trends and regional variation in opioid overdose mortality among Veterans Health Administration patients, fiscal year 2001 to 2009. *Clin J Pain*. 2014; 30(7): 605-612.

63. Dhalla IA, Mamdani MM, Sivilotti MLA, Kopp A, Qureshi O, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ*. 2009; 181(12): 891-896.
64. Fischer B, Jones W, Urbanoski K, Skinner R, Rehm J. Correlations between prescription opioid analgesic dispensing levels and related mortality and morbidity in Ontario, Canada, 2005–2011. *Drug Alcohol Rev*. 2014; 33(1): 19-26.
65. Modarai F, Mack K, Hicks P, Benoi S, Park S, et al. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug Alcohol Depend*. 2013; 132(1–2): 81-86.
66. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med*. 2015; 372(3): 241-248.
67. Center for Behavioral Health Statistics and Quality. Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health. 2015; <http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf>. Accessed 23 July 2016.
68. Paulozzi LJ. Prescription drug overdoses: a review. *J Safety Res*. 2012; 43(4): 283-289.
69. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA*. 2013; 309(7): 657-659.
70. Coben JH, Davis SM, Furbee PM, Sikora RD, Tillotson RD, et al. Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers. *Am J Prev Med*. 2010; 38(5): 517-524.
71. Kuehn BM. Alarming nonfatal overdose rates found for opioids, sedatives, and tranquilizers. *JAMA*. 2010; 303(20): 2020-2021.

72. Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. *NCHS Data Brief*. 2009; (22): 1-8.
73. Inocencio TJ, Carroll NV, Read EJ, Holdford DA. The economic burden of opioid-related poisoning in the United States. *Pain Med*. 2013; 14(10): 1534-1547.
74. Tadros A, Layman SM, Davis SM, Davidov DM, Cimino S. Emergency visits for prescription opioid poisonings. *J Emerg Med*. 2015; 49(6): 871-877.
75. Hasegawa K, Espinola JA, Brown DFM, Camargo CA. Trends in U.S. emergency department visits for opioid overdose, 1993–2010. *Pain Med*. 2014; 15(10): 1765-1770.
76. Ronan MV, Herzig SJ. Hospitalizations related to opioid abuse/dependence and associated serious infections increased sharply, 2002–12. *Health Aff*. 2016; 35(5): 832-837.
77. Unick GJ, Rosenblum D, Mars S, Ciccarone D. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993-2009. *PLoS ONE*. 2013; 8(2): e54496.
78. Chandwani HS, Strassels SA, Rascati KL, Lawson KA, Wilson JP. Estimates of charges associated with emergency department and hospital inpatient care for opioid abuse-related events. *J Pain Palliat Care Pharmacother*. 2013; 27(3): 206-213.
79. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths - United States, 2000-2014. *MMWR Morb Mortal Wkly Rep*. 2016; 64(50-51): 1378-1382.
80. Sharp MJ, Melnik TA. Poisoning deaths involving opioid analgesics — New York State, 2003–2012. *MMWR Morb Mortal Wkly Rep*. 2015; 64(14): 377-380.

81. Chen LH, Hedegaard H, Warner M. Drug-poisoning deaths involving opioid analgesics: United States, 1999-2011. *NCHS Data Brief*. 2014; (166): 1-8.
82. Visconti AJ, Santos G-M, Lemos NP, Burke C, Coffin PO. Opioid overdose deaths in the city and county of San Francisco: prevalence, distribution, and disparities. *J Urban Health*. 2015; 92(4): 758-772.
83. Warner M, Hedegaard H, Chen L. Trends in drug-poisoning deaths involving opioid analgesics and heroin: United States, 1999–2012. *NCHS Health E-Stat*. 2014; [www.cdc.gov/nchs/data/hestat/drug\\_poisoning/drug\\_poisoning\\_deaths\\_1999-2012.pdf](http://www.cdc.gov/nchs/data/hestat/drug_poisoning/drug_poisoning_deaths_1999-2012.pdf). Accessed 23 July 2016.
84. Calcaterra S, Glanz J, Binswanger IA. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999–2009. *Drug Alcohol Depend*. 2013; 131(3): 263-270.
85. Cerdá M, Ransome Y, Keyes KM, Koenen KC, Tracy M, et al. Prescription opioid mortality trends in New York City, 1990–2006: examining the emergence of an epidemic. *Drug Alcohol Depend*. 2013; 132(1): 53-62.
86. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb Mortal Wkly Rep*. 2011; 60(43): 1487-1492.
87. White AG, Birnbaum HG, Mareva MN, DAher M, Vallow S, et al. Direct costs of opioid abuse in an insured population in the United States. *J Manage Care Pharm*. 2005; 11(6): 469-479.
88. Oderda GM, Lake J, Rudell K, Roland CL, Masters ET. Economic burden of prescription opioid misuse and abuse: a systematic review. *J Pain Palliat Care Pharmacother*. 2015; 29(4): 388-400.

89. White A, Birnbaum H, Schiller M, Waldman T, Cleveland J, et al. Economic impact of opioid abuse, dependence, and misuse. *Am J Pharm Benefits*. 2011; 3(4): e59-70.
90. Pasquale MK, Joshi AV, Dufour R, Schaaf D, Mardekian, et al. Cost drivers of prescription opioid abuse in commercial and Medicare populations. *Pain Pract*. 2014; 14(3): E116-125.
91. McAdam-Marx C, Roland CL, Cleveland J, Oderda GM. Costs of opioid abuse and misuse determined from a Medicaid database. *J Pain Palliat Care Pharmacother*. 2010; 24(1): 5-18.
92. Strassels S. Economic burden of prescription opioid misuse and abuse. *J Manag Care Pharm*. 2009; 15(7): 556-562.
93. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, et al. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med*. 2011; 12(4): 657-667.
94. Birnbaum HG, White AG, Reynolds JL, Greenberg PE, Zhang M, et al. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. *Clin J Pain*. 2006; 22(8): 667-676.
95. World Health Organization. Essential medicines and health products. 2016; [http://www.who.int/medicines/services/essmedicines\\_def/en/](http://www.who.int/medicines/services/essmedicines_def/en/). Accessed 27 June 2016.
96. Gladstone EJ, Smolina K, Morgan SG. Trends and sex differences in prescription opioid deaths in British Columbia, Canada. *Inj Prev*. 2016; 22(4): 288-290.
97. Murphy Y, Goldner EM, Fischer B. Prescription opioid use, harms and interventions in Canada: a review update of new developments and findings since 2010. *Pain Physician*. 2015; 18(4): E605-614.

98. Giraudon I, Lowitz K, Dargan PI, Wood DM, Dart RC. Prescription opioid abuse in the UK. *Br J Clin Pharmacol*. 2013; 76(5): 823-824.
99. Roxburgh A, Hall WD, Burns L, Pilgrim J, Saar E, et al. Trends and characteristics of accidental and intentional codeine overdose deaths in Australia. *Med J Aust*. 2015; 203(7): 299-299.
100. Barrett SP, Meisner JR, Stewart SH. What constitutes prescription drug misuse? Problems and pitfalls of current conceptualizations. *Curr Drug Abuse Rev*. 2008; 1(3): 255-262.
101. Heit HA, Gourlay DL. Tackling the difficult problem of prescription opioid misuse. *Ann Intern Med*. 2010; 152(11): 747-748.
102. Nelson LS, Paulozzi LJ. The toxicology tower of Babel: why we need to agree on a lexicon in prescription opioid research. *J Med Toxicol*. 2012; 8(4): 331-332.
103. Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTION systematic review and recommendations. *Pain*. 2013; 154(11): 2287-2296.
104. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, et al. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend*. 2003; 69(3): 215-232.
105. Savage SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, et al. Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Manage*. 2003; 26(1): 655-667.
106. Davies A, Webber K. Misuse of rapid-onset opioids? Misuse of terminology! *Palliat Med*. 2016; 30(5): 513-514.
107. Sullivan M. Clarifying opioid misuse and abuse. *Pain*. 2013; 154(11): 2239-2240.

108. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, et al. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009; 10(2): 131-146.
109. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*. Vol 1: World Health Organization; 2004.
110. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Vol 4, 1994: American Psychiatric Association; 2000.
111. Campbell G, Bruno R, Lintzeris N, Cohen M, Nielsen S, et al. Defining problematic pharmaceutical opioid use among people prescribed opioids for chronic noncancer pain: do different measures identify the same patients? *Pain*. 2016; 157(7): 1489-1498.
112. Degenhardt L, Bruno R, Lintzeris N, Hall W, Nielsen S, et al. Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study. *Lancet Psychiatry*. 2015; 2(4): 314-322.
113. Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. *Pain Med*. 2009; 10(8): 1426-1433.
114. Butler SF, Budman SH, Fernandez K, Jamison RN. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain*. 2004; 112(1-2): 65-75.
115. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005; 6(6): 432-442.

116. Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, et al. Development and validation of the current opioid misuse measure. *Pain*. 2007; 130(1): 144-156.
117. Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, et al. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain*. 2007; 23(4): 307-315.
118. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain*. 2008; 24(6): 497-508.
119. Parafloo K. Questionnaires: use, value and limitations. *Nurse Res*. 1994; 1(2): 4-11.
120. Furu K. Establishment of the nationwide Norwegian Prescription Database (NorPD)—new opportunities for research in pharmacoepidemiology in Norway. *Norsk Epidemiol*. 2009; 18(2): 129-136.
121. Braker LS, Reese AE, Card RO, Van Howe RS. Screening for potential prescription opioid misuse in a Michigan Medicaid population. *Fam Med*. 2009; 41(10): 729.
122. Do Quang-Cantagrel N, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. *Anesth Analg*. 2000; 90(4): 933-937.
123. Coyne KS, LoCasale RJ, Datto CJ, Sexton CC, Yeomans K, et al. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and retrospective chart review. *Clinicoecon Outcomes Res*. 2014; 6: 269-281.
124. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review. *J Clin Psychiatry*. 2010; 71(4): 491-496.

125. Hennessy S. Use of health care databases in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006; 98(3): 311-313.
126. Jorm L. Routinely collected data as a strategic resource for research: priorities for methods and workforce. *Public Health Res Prac*. 2015; 25(4): e2541540.
127. Wettermark B, Zoega H, Furu K, Korhonen M, Hallas J, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research—a literature review. *Pharmacoepidemiol Drug Saf*. 2013; 22(7): 691-699.
128. Avorn J. In defense of pharmacoepidemiology—embracing the yin and yang of drug research. *N Engl J Med*. 2007; 357(22): 2219-2221.
129. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects—advantages and disadvantages. *Nat Clin Pract Rheumatol*. 2007; 3(12): 725-732.
130. Wettermark B, Hammar N, MichaelFored C, Laimanis A, Otterblad Olausson P, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007; 16(7): 726-735.
131. Fleurence RL, Naci H, Jansen JP. The critical role of observational evidence in comparative effectiveness research. *Health Aff*. 2010; 29(10): 1826-1833.
132. Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. *Pharmacoepidemiol Drug Saf*. 2008; 17(3): 215-223.
133. Harpe SE. Using secondary data sources for pharmacoepidemiology and outcomes research. *Pharmacotherapy*. 2009; 29(2): 138-153.

134. Garcia del Pozo J, Carvajal A, Viloria JM, Velasco A, Garcia del Pozo V. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *Eur J Clin Pharmacol.* 2008; 64(4): 411-415.
135. Hudec R, Tisonova J, Bozekova L, Foltan V. Trends in consumption of opioid analgesics in Slovak Republic during 1998-2002. *Eur J Clin Pharmacol.* 2004; 60(6): 445-448.
136. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995–2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain.* 2015; 19(1): 59-66.
137. Schubert I, Ihle P, Sabatowski R. Increase in opiate prescription in Germany between 2000 and 2010. *Dtsch Arztebl Int.* 2013; 110(4): 45-51.
138. Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, et al. Sex differences in dose escalation and overdose death during chronic opioid therapy: a population-based cohort study. *PLoS ONE.* 2015; 10(8): e0134550.
139. Hwang CS, Chang HY, Alexander GC. Impact of abuse-deterrent OxyContin on prescription opioid utilization. *Pharmacoepidemiol Drug Saf.* 2014; 24(2): 197-204.
140. Franklin GM, Mai J, Turner J, Sullivan M, Wickizer T, et al. Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline. *Am J Ind Med.* 2012; 55(4): 325-331.
141. Peirce GL, Smith MJ, Abate MA, Halverson J. Doctor and pharmacy shopping for controlled substances. *Med Care.* 2012; 50(6): 494-500.
142. Katz N, Panas L, Kim M, Audet AD, Bilanksy A, et al. Usefulness of prescription monitoring programs for surveillance—analysis of Schedule II opioid prescription

- data in Massachusetts, 1996–2006. *Pharmacoepidemiol Drug Saf.* 2010; 19(2): 115-123.
143. Cepeda MS, Fife D, Ma Q, Ryan PB. Comparison of the risks of opioid abuse or dependence between tapentadol and oxycodone: results from a cohort study. *J Pain.* 2013; 14(10): 1227-1241.
144. Chenaf C, Kabore JL, Delorme J, Pereira B, Mulliez A, et al. Incidence of tramadol shopping behavior in a retrospective cohort of chronic non-cancer pain patients in France. *Pharmacoepidemiol Drug Saf.* 2016; 25(9): 1088-1098.
145. Gadzhanova S, Bell JS, Roughead EE. What analgesics do older people use prior to initiating oxycodone for non-cancer pain? A retrospective database study. *Drugs Aging.* 2013; 30(11): 921-926.
146. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011; 171(7): 686-691.
147. Baumblatt J, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, et al. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. *JAMA Intern Med.* 2014; 174(5): 796-801.
148. Bohnert AB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA.* 2011; 305(13): 1315-1321.
149. Martyres RF, Clode D, Burns JM. Seeking drugs or seeking help? Escalating "doctor shopping" by young heroin users before fatal overdose. *Med J Aust.* 2004; 180(5): 211-214.

150. Australian Bureau of Statistics. Characteristics of bodily pain in Australia. 2012;  
<http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4841.0Chapter12011>. Accessed 3 August 2016.
151. MBF Foundation. *The high price of pain: the economic impact of persistent pain in Australia*. 2007.  
[http://www.bupa.com.au/staticfiles/BupaP3/Health%20and%20Wellness/MediaFiles/PDFs/MBF\\_Foundation\\_the\\_price\\_of\\_pain.pdf](http://www.bupa.com.au/staticfiles/BupaP3/Health%20and%20Wellness/MediaFiles/PDFs/MBF_Foundation_the_price_of_pain.pdf). Accessed 1 June 2017.
152. Australian Institute of Health and Welfare. *Drugs in Australia 2010: tobacco, alcohol and other drugs*. Canberra: Australian Institute of Health and Welfare; 2011.
153. Australian Institute of Health and Welfare. *National Drug Strategy Household Survey detailed report: 2013*. Canberra: Australian Institute of Health and Welfare; 2014.
154. Australian Institute of Health and Welfare. *2010 National Drug Strategy Household Survey Report*. Canberra: Australian Institute of Health and Welfare; 2011.
155. Australian Bureau of Statistics. *National Survey of Health and Wellbeing: Summary of results*. Australia. 2007;  
<http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/4326.0Main%20Features32007?opendocument&tabname=Summary&prodno=4326.0&issue=2007&num=&view=>. Accessed 20 July 2016.
156. Biggs A. *Medicare - Background Brief*. 2003;  
[http://www.aph.gov.au/About\\_Parliament/Parliamentary\\_Departments/Parliamentary\\_Library/Publications\\_Archive/archive/medicare](http://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/Publications_Archive/archive/medicare). Accessed 15 August 2016.
157. Australian Government Department of Health. *About the PBS*. 2016;  
<http://www.pbs.gov.au/info/about-the-pbs>. Accessed 13 June 2016.

158. Australian Government Department of Health Therapeutic Goods Administration. Evaluation of a new medicine - the TGA's lifecycle approach to regulation. 2011; <https://www.tga.gov.au/node/1064>. Accessed 15 August 2016.
159. Australian Government Department of Health. Australian statistics on medicines 2014. 2016; <http://www.pbs.gov.au/info/statistics/asm/asm-2014 - Toc425339252>. Accessed 3 August 2016.
160. World Health Organization Collaborating Centre for Drug Statistics Methodology. Structure and principles. 2011; [http://www.whocc.no/atc/structure\\_and\\_principles/](http://www.whocc.no/atc/structure_and_principles/). Accessed 26 June 2016.
161. Kemp A, Paige E, Banks E. Beginner's guide to using Pharmaceutical Benefits Scheme data: tips and pitfalls. 2013; [http://nceph.anu.edu.au/files/Guide\\_to\\_Using\\_PBS\\_Data\\_20131125](http://nceph.anu.edu.au/files/Guide_to_Using_PBS_Data_20131125), 17 March 2016.
162. Australian Government Department of Health. Pharmaceutical benefits: fees, patient contributions and safety net thresholds. 2016; <http://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee>. Accessed 31 May 2016.
163. Australian Government Department of Health. The Safety Net Scheme. 2016; [http://www.pbs.gov.au/info/healthpro/explanatory-notes/section1/Section\\_1\\_5\\_Explanatory\\_Notes](http://www.pbs.gov.au/info/healthpro/explanatory-notes/section1/Section_1_5_Explanatory_Notes). Accessed 31 May 2016.
164. The Pharmacy Guild of Australia. About the guild. 2015; <https://www.guild.org.au/the-guild/about-the-guild>. Accessed 26 July 2016.
165. Australian Government Department of Human Services. Prescribing in public hospital participating in the Pharmaceutical Reforms. 2016;

<http://medicareaust.com/Accessible/PBS/PrescribinginPublicHospitals/WCAGWelcome/index.html>. Accessed 18 September 2016.

166. Cairns R, Brown JA, Buckley NA. The impact of codeine re - scheduling on misuse: a retrospective review of calls to Australia's largest poisons centre. *Addiction*. 2016; 111(10): 1848-1853.
167. McAvoy BR, Dobbin MD, Tobin CL. Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand. *N Z Med J*. 2011; 124(1346): 29-33.
168. Gisev N, Nielsen S, Cama E, Larance B, Bruno R, Degenhardt L. An ecological study of the extent and factors associated with the use of prescription and over-the-counter codeine in Australia. *Eur J Clin Pharmacol*. 2016; 72(4): 469-494.
169. Nicholas R, Lee N, Roche A. *Pharmaceutical drug misuse problems in Australia: complex problems, balanced responses*. Flinders University, Australia: National Centre for Education and Training on Addiction (NCETA);2011.
170. Pearson S-A, Pesa N, Langton JM, Drew A, Faedo M, Robertson J. Studies using Australia's Pharmaceutical Benefits Scheme data for pharmacoepidemiological research: a systematic review of the published literature (1987–2013). *Pharmacoepidemiol Drug Saf*. 2015; 24(5): 447-455.
171. Bell JR. Australian trends in opioid prescribing for chronic non-cancer pain, 1986-1996. *Med J Aust*. 1997; 167(1): 26-29.
172. Berbatis CG, Sunderland VB, Bulsara M, Lintzeris N. Trends in licit opioid use in Australia, 1984-1998: comparative analysis of international and jurisdictional data. *Med J Aust*. 2000; 173(10): 524-527.

173. Hollingworth SA, Gray PD, Hall WD, Najman JM. Opioid analgesic prescribing in Australia: a focus on gender and age. *Pharmacoepidemiol Drug Saf.* 2015; 24(6): 628-636.
174. Hollingworth SA, Symons M, Khatun M, Loveday B, Ballantyne S, et al. Prescribing databases can be used to monitor trends in opioid analgesic prescribing in Australia. *Aust N Z J Public Health.* 2013; 37(2): 132-138.

**Chapter Two: Harmonising post-market surveillance of prescription drug misuse: a systematic review of observational studies using routinely collected data (2000-2013)**

To quantify the extent of population prescription drug misuse we first need to understand how this concept is defined across jurisdictions. Consequently, in this chapter we present the results of a global systematic review investigating the extent and methods of quantifying prescription drug misuse through pharmaceutical claims.

This chapter is based on the following publication:

Bianca Blanch, Nicholas A. Buckley, Leigh Mellish, Andrew H. Dawson, Paul S. Haber, Sallie-Anne Pearson. Harmonizing post-market surveillance of prescription drug misuse: a systematic review of observational studies using routinely collected data (2000-2013). *Drug Safety*. 2015; 38: 553-564.

Formatting note: To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. The key points and abstract are formatted according to the *Drug Safety* style guide. We provide the reference list at the end of this chapter. Due to the length of the supplementary materials for this chapter we provide them in Appendix A only.

## ***Key Points***

- Prescription drug misuse is increasing globally. This can be readily monitored using routinely collected data to quantify drug access patterns at the population-level.
- Our review identified only four common proxies for prescription drug misuse (number of prescribers, number of dispensing pharmacies, volume of drug[s] dispensed and/or overlapping prescriptions/early refills); however, these proxies were used to derive 89 unique definitions of drug misuse due to variations in thresholds or measures (single or multiple behaviour measures).
- We recommend the development of consistent and replicable metrics to facilitate monitoring and comparisons of the extent of prescription drug misuse across healthcare settings and over time.

## ***Abstract***

### *Background*

Prescription drug misuse is a growing public health concern globally. Routinely collected data provide a valuable tool for quantifying prescription drug misuse.

### *Objective*

To synthesise the global literature investigating prescription drug misuse utilising routinely collected, person-level prescription/dispensing data to examine reported measures, documented extent of misuse and associated factors.

### *Methods*

The MEDLINE, EMBASE, CINAHL, MEDLINE In Process, Scopus citations and Google Scholar databases were searched for relevant articles published between 1 January 2000 and 31 July 2013. A total of 10 803 abstracts were screened and 281 full-text manuscripts were retrieved. Fifty-two peer-reviewed, English language manuscripts met our inclusion criteria—an aim/method investigating prescription drug misuse in adults and a measure of misuse derived exclusively from prescription/dispensing data.

### *Results*

Four proxies of prescription drug misuse were commonly used across studies: number of prescribers, number of dispensing pharmacies, early refills and volume of drugs dispensed. Overall, 89 unique measures of misuse were identified across the 52 studies, reflecting the heterogeneity in how measures are constructed: single or composite; different thresholds, cohort definitions and time period of assessment. Consequently, it was not possible to make

definitive comparisons about the extent (range reported 0.01–93.5%), variations and factors associated with prescription drug misuse.

### *Conclusions*

Routine data collections are relatively consistent across jurisdictions. Despite the heterogeneity of the current literature, our review identifies the capacity to develop universally accepted metrics of misuse applied to a core set of variables in prescription/dispensing claims. Our timely recommendations have the potential to unify the global research field and increase the capacity for routine surveillance of prescription drug misuse.

## **2.1 Introduction**

Research demonstrates a high degree of variability in how drugs are prescribed and used.<sup>1</sup> Prescription drugs including sedatives, anxiolytics, analgesics and stimulants are often taken excessively to enhance desired effects.<sup>1</sup> The consequences of excessive use are a major public health concern and include drug tolerance,<sup>2,3</sup> increased risk of side effects,<sup>3-5</sup> overdose,<sup>6</sup> dependence,<sup>7</sup> hospitalisation,<sup>5</sup> or death.<sup>2,8,9</sup> These risks are escalated with concomitant prescription drug, alcohol or illicit drug use.<sup>10-16</sup>

Research methodologies, including medical chart review,<sup>17</sup> surveys,<sup>18</sup> qualitative,<sup>19,20</sup> and observational studies,<sup>21</sup> have been used to explore prescription drug misuse. In recent decades, the growing availability of routinely collected health information has increased opportunities to undertake population-based surveillance of prescription drugs. The evidence generated from routinely collected data can further enhance our understanding of prescription drug misuse, patient and prescriber behaviour outcomes of misuse, and influence policy changes on these issues.

There are no universally accepted definitions of prescription drug misuse<sup>22,23</sup> making quantification challenging. Due to the limited clinical information held in routine data collections, prescription drug misuse is not directly measured at the population level<sup>23</sup> but is commonly inferred based on patterns of drug access and by investigating patient interactions with prescribers and pharmacies.

In response to concerns about the management of chronic pain treated with opioid analgesics, the US Food and Drug Administration (FDA) has recently sought submissions

related to the post-market surveillance of extended release and long-acting opioid formulations.<sup>24</sup> In particular, the FDA requested submissions relating to defining misuse, abuse, addiction and their consequences measured in routine data collections.<sup>24</sup> Clearly, synthesising the global literature will add significant value to this endeavour.

Our timely systematic review aims to examine the measures, extent and factors associated with prescription drug misuse in observational studies based on routinely collected person-level prescription or dispensing data.

## **2.2 Methods**

### *2.2.1 Eligible studies*

Our review included English-language, peer-reviewed manuscripts published between 1 January 2000 and 31 July 2013, which satisfied the following criteria:

- aim or method investigated prescription drug misuse;
- measure of prescription drug misuse derived exclusively from person-level prescription/dispensing data;
- investigated misuse in adult persons ( $\geq 18$  years).

We excluded grey literature (government reports), case reports, letters, editorials, opinion pieces, reviews and conference abstracts.

### *2.2.2 Study identification*

Search strategy (Supplementary Material [SM] 1)

A search was conducted of the MEDLINE, EMBASE, CINAHL and MEDLINE In Process databases combining keywords and subject headings to identify studies investigating prescription drug misuse measured in routinely collected prescription/dispensing data using observational approaches. Search terms included misuse; problematic; prescription drugs; factual databases; population surveillance and cohort studies. Three further searches were completed using Google Scholar<sup>25</sup> (we reviewed first 200 results per search), Scopus citations (for articles citing included manuscripts) and screened back references of included studies, review articles and selected excluded studies.

Two reviewers (BB and LM) screened the abstracts and titles of articles to identify potentially relevant studies. These studies were assessed independently (BB and LM) for inclusion in the review using a five-item tool based on the eligibility criteria (SM 2). A third reviewer (SP) arbitrated when consensus about inclusion was not reached (18% of articles).

### *2.2.3 Data extraction*

Two independent reviewers (BB and LM) completed comprehensive data extraction for articles meeting our eligibility criteria (SM 3), with the following information being extracted:

1. Study characteristics: year of publication; publishing journal; observation period (beginning and end year, and duration in months); funding source; objectives; setting; generic names of prescription drug(s) investigated; data source; including extent of population coverage and terminology related to misuse. We also calculated lag time (year of publication minus last year of observation).

2. Cohort characteristics: number of cohort(s); cohort size(s) and cohort details, including study inclusion/exclusion criteria. Studies reported the extent of prescription drug misuse in drug-user cohorts (persons dispensed or prescribed the drug[s] of interest) or in misuse cohorts (persons exhibiting behaviour considered to be above the norms of prescription drug use).

3. Measures of prescription drug misuse: the characteristic or behaviour of interest (e.g. number of prescribers), threshold defining behaviour indicative of misuse as defined by the study authors (e.g.  $\geq 4$  prescribers) and time period of assessment (e.g. 6 months). Each measure was identified as follows:

- stand-alone: investigated a single characteristic or behaviour (e.g. the proportion of persons accessing ' $\geq 4$  prescribers' in 6 months); or
- composite: in drug-user cohorts, the measurement of two or more characteristics or behaviours (e.g. the proportion of persons using ' $\geq 4$  prescribers AND  $\geq 4$  dispensing pharmacies' in 6 months). In misuse cohorts (e.g. defined by persons visiting ' $\geq 4$  prescribers' in 6 months) the measurement of at least one additional characteristic or behaviour (e.g. the proportion of misusers accessing ' $\geq 4$  dispensing pharmacies' in 6 months).

4. Other prescription drug misuse-related outcomes, e.g. dispensed specific drug classes or drugs associated with misuse.

5. Summary statistics: percentages or other statistics (e.g. means with standard deviation or medians with ranges) related to all misuse measures. Where possible, we calculated the extent of misuse in user cohorts if not reported in individual studies.

6. Rationale for measure(s) of misuse: any reference to previously published studies; expert panel recommendations; empirical derivation, or any other rationale.

7. Comprehensiveness of reporting (BB only) according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement Checklist for Observational, Population-Based Cohort Studies.<sup>26,27</sup>

#### *2.2.4 Terminology*

In the global literature, a range of terms are used to encapsulate prescription drug misuse including abuse, dependence, diversion, misuse, extramedical, problematic or non-medical use.<sup>1,28-30</sup> As such, our search strategies included 24 unique misuse-related terms to capture relevant articles. For the purposes of this review, we use the umbrella term 'prescription drug misuse' to capture the continuum of misuse, ranging from use above the norms, through to dependence, abuse and diversion. This is consistent with the FDA's terminology in their recent call for submissions on post-market opioid surveillance.<sup>24</sup>

#### *2.2.5 Analysis*

In reviewed studies there was considerable variation in study design including: study population(s), drug(s) of interest, definition(s) of misuse and outcome measures. Due to this variation, it was not possible or appropriate to use traditional meta-analytic approaches to pool individual study results. Instead, we provide a descriptive analysis, detail the key findings of individual studies and summarise study features in tables and figures. Our review is consistent with AMSTAR (A Measurement Tool to Assess Systematic Reviews) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting criteria (SM 4).

## **2.3 Results**

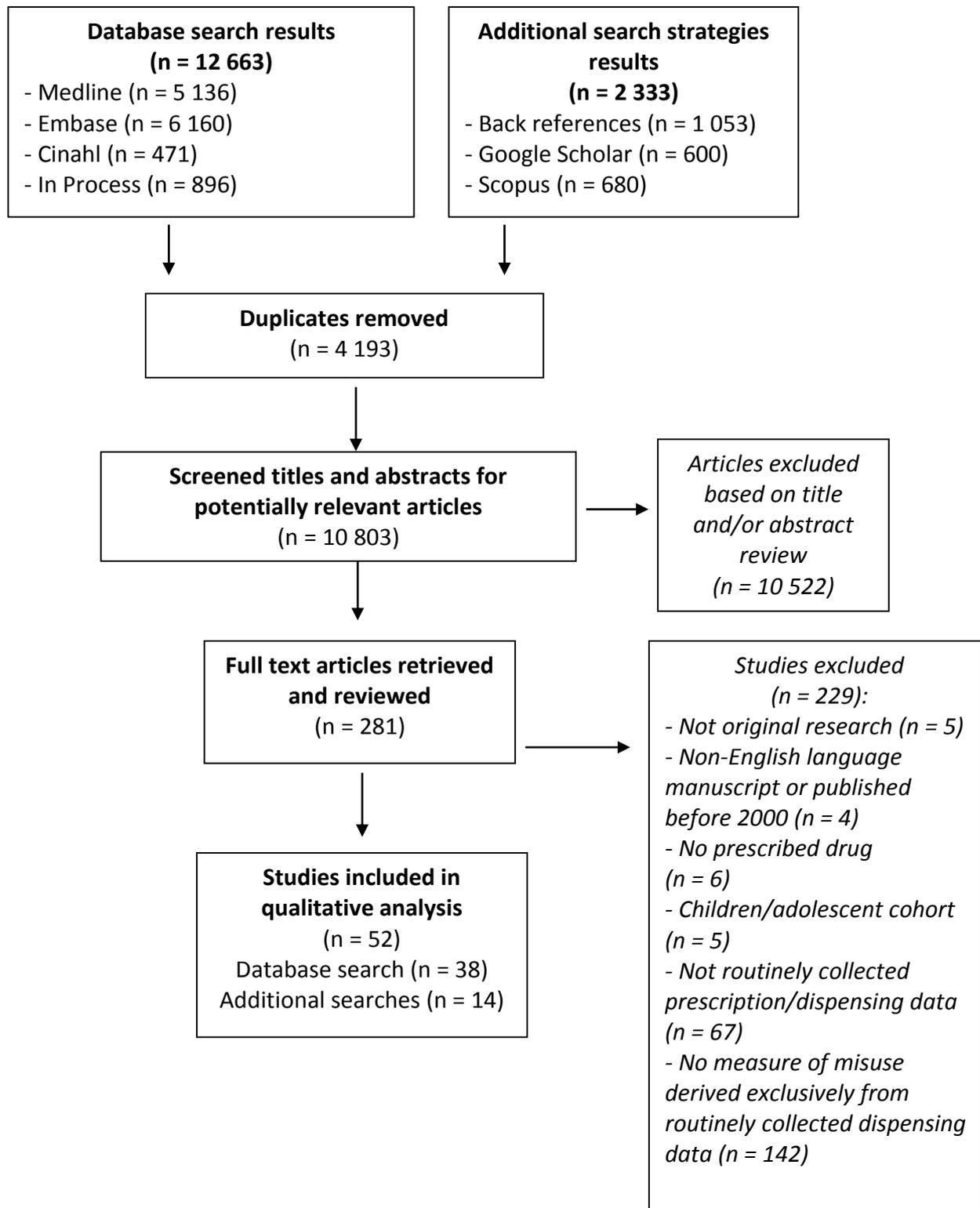
### *2.3.1 Studies identified*

The titles/abstracts of 10 803 articles were screened and 281 full-text manuscripts were reviewed. Fifty-two studies met our eligibility criteria; 38 were identified from MEDLINE, EMBASE, CINAHL or MEDLINE In Process, two from Google Scholar, four from Scopus citations and eight from back references (Figure 2.1). The bibliography of the 229 excluded and 52 included studies are detailed in SM 5 and 6, respectively.

### *2.3.2 Study features*

The studies were set in the US (27 studies), France (17 studies), Norway (seven studies) or Canada (one study) (Table 2.1; SM 7). All studies from Norway used dispensing data for the entire national population; the remaining 45 studies used populations within a specific province, state or region. Of the 52 included studies, 32 (61.5%) were published between 2010 and July 2013. The median study observation period was 18 months (range: 4–132 months; interquartile range [IQR]: 12–37.5 months) and the median lag time was 4 years (range: 2–15 years; IQR: 3–6 years). Twenty-one studies did not report a funding source, and the remaining studies were funded primarily by research grants (15 studies) or the pharmaceutical industry (seven studies). Fifty-one studies utilised dispensing data; one study used prescription data. Forty-six unique terms were used by study authors to encapsulate the concept of ‘prescription drug misuse’ (Box 2.1).

**Figure 2.1.** Flow chart of systematic review methodology to identify included manuscripts



**Table 2.1** Characteristics of included studies (N= 52 studies)

	N	%
Study setting		
United States	27	51.9
France	17	32.7
Norway	7	13.5
Canada	1	1.9
Year of publication		
2000-2004	7	13.5
2005-2009	13	25.0
2010-2013	32	61.5
Length of observation period for routinely collected data		
<12 months	5	9.6
12 months to 24 months (inclusive)	28	53.8
25 months to 48 months (inclusive)	11	21.2
49 months to 108 months (inclusive)	7	13.5
>108 months	1	1.9
Publication lag (year published - last year of observation)		
1-2 years	4	7.7
3-5 years	34	65.4
6-10 years	8	15.4
>10 years	6	11.5
Study funding		
Grants: government, non-government or research	15	28.8
Industry: pharmaceutical company	7	13.5
Core government funding	3	5.8
Other	4	7.7
No funding	2	3.8
Not disclosed	21	40.4
Number of prescription drug classes investigated per study		
One	39	75.0
Two	5	9.6
Three	6	11.5
Four	2	3.8
Drug classes investigated for misuse <sup>a</sup>		
Opioids (includes controlled substances)	35	46.1
Benzodiazepine	20	26.3
Z-drug (zopiclone; zolpidem)	5	6.6
Antidepressant	4	5.3
Other sedative (carisoprodol)	4	5.3
Central nervous system stimulant	3	3.9
Anorectic (diuretic)	2	2.6
Anticholinergic antiparkinson drug	1	1.3

Antipsychotic	1	1.3
Psychotropic (not further specified)	1	1.3

---

<sup>a</sup> 13 studies investigated more than one drug class; % represents prevalence of each drug class studied (denominator of 76)

**Box 2.1** Terminology used in reviewed studies to describe prescription drug misuse

We noted 46 different terms including: abuser, clinical abuser, decedent, dependence, deviant (behaviour), deviant consumer, doctor shopper/shopping, excess use, excessive dose, excessive use, excessive user, extreme population, forgery behaviour, fraudulent behaviour, heavy shopper, high consumer, high risk use, high usage, high user, inappropriate dispensing, inappropriate prescription, inappropriate use, long term user, misuse, moderate user, multiple prescriber episode, occasional user, overconsumption, overconsumer, overutilisation, persistent use(r), pharmacy hopping, pharmacy shopper, potentially aberrant, potentially inappropriate use, potentially problematic use, probably problematic behaviour, problematic use(r), putative acceptable use, questionable activity, recurrent user, repeat user, shopper, shopping behaviour, transgression behaviour, or user.

### 2.3.2.1 Prescription drugs of interest

All studies specified the drug class(es) of interest; the majority focused on opioids (35 studies) and/or benzodiazepines (20 studies) (Table 2.1). Twenty-nine studies further detailed the specific drugs of interest; the most commonly investigated drugs were codeine (ten studies) and/or diazepam (nine studies). Eleven studies investigated a single drug, five of which focused on buprenorphine, for the indications of opiate maintenance therapy or pain.

### 2.3.2.2 Cohort characteristics

Thirty-nine studies investigated misuse in a drug-user cohort (dispensed drug of interest); 17 in a misuse cohort (authors determined drug use or access pattern of cohort to be above the norms), 14 included both cohort types, and one did not define the user group.

Approximately 93 million prescription drug-users were observed across the studies with considerable variability in cohort size (<100 persons to >25 million persons). Twenty-six studies used a comparison cohort differing from the other cohort most commonly due to the drug of interest (nine studies); nature, degree or extent of misuse (seven studies) or region of residence (five studies). Two studies matched the cohorts on specific variables, including month of index prescription, geographic area of dispensing pharmacy, prescriber specialty, age and/or number of prescriptions (total and for drugs with abuse potential).

### 2.3.3 Measures of prescription drug misuse

Fifty studies defined a measure with a specific misuse threshold (e.g.  $\geq 4$  prescribers) (Table 2.2; SM 8). Overall, four metrics were the basis of the misuse measures, either alone or in

combination: number of prescribers, number of dispensing pharmacies, volume of drug(s) dispensed and/or overlapping prescriptions/early refills.

Twenty-four studies used at least one stand-alone measure of misuse, 46 studies used at least one composite measure of misuse and 20 studies used both types of measures. Of the 46 studies that used a composite measure, only five reported the proportion of the cohort exhibiting each component of a composite measure.<sup>31-35</sup> The other studies did not detail the relative contribution of each component to the extent of misuse.

#### *2.3.4 The extent of prescription drug misuse*

The extent of misuse ranged from 0.01 to 93.5%, and was generally higher for stand-alone measures compared with composite measures (for the latter, individuals needed to exhibit at least two characteristics or behaviours, as opposed to one) (SM 8). The variability in the extent of misuse reported across the studies reflected the heterogeneity in methodology; more specifically, measures and thresholds of misuse, cohort definition and the time period of assessment.

##### *2.3.4.1 Measures and thresholds of misuse*

Overall, 89 unique definitions of misuse were identified across 50 studies; only 13 measures were utilised in two or more studies (32 studies in total). There appeared to be an attempt to use pre-existing measure(s) of misuse within, but not between, research groups; however, some groups changed their misuse measures between studies.

**Table 2.2** Summary of measures with a defined threshold of prescription drug misuse (N=50 studies)

<b>Measure details (author-defined threshold of misuse behaviour)</b>	<b>Stand-alone measure (24 studies)</b>	<b>References</b>	<b>Metric used in composite measure (46 studies)</b>	<b>References</b>	<b>Total<sup>a</sup></b>
Number of prescribers (mode: 4; range: 2-7)	9	37, 44, 64-70	32	16, 34, 37, 39-43, 45-48, 65, 67, 68, 70-86	36
Number of dispensing pharmacies (mode: 4; range: 2-4)	10	36, 37, 64, 67-70, 87-89	25	34, 36, 37, 39-41, 43, 46, 48, 67, 68, 70-73, 75, 78-82, 85, 86, 88, 90	29
Volume of drug dispensed (including number of dispensings, and dispensed DDD)	14	35, 38, 65, 67-69, 85, 87, 88, 91-95	23	36, 38, 46, 65-68, 70, 72, 73, 75, 77, 79, 80, 82-85, 88, 90-92, 94	28
Overlapping prescriptions or early refills	6	34, 35, 39, 68, 95, 96	21	35, 39, 42, 43, 45-47, 68, 69, 71, 74-78, 81, 85-87, 95, 96	22
Use of specific prescribed drug (e.g. alprazolam)	3	35, 69, 87	6	35, 69, 72, 73, 87, 95	6
Duration of prescription drug use (e.g. >120 days use)	2	87, 95	2	36, 69	4
Dose escalation (e.g. 50% dosage increase in mean mg of drug in 2 months)	2	68, 89	1	68	2
Other (Latent analysis based on age, sex and method of payment)	0	-	1	97	1

DDD: defined daily dose; mg: milligrams

<sup>a</sup> Number of unique studies investigating behaviour as a stand-alone and/or composite measure of misuse

Sixteen studies reported the number of prescribers and/or dispensing pharmacies accessed routinely by prescription drug-users. As thresholds increased, the proportion of the population exhibiting the behaviour decreased (Figures 2.2A and 2.2B). Importantly, the highest proportion of drug-users visited 1–2 prescribers or pharmacies when accessing their drug(s). Thirteen of these studies defined a threshold of misuse; nine studies (69.2%) set the threshold of misuse as  $\geq 3$  prescribers or dispensing pharmacies. The thresholds defining misuse impacts on the extent of the problem reported across studies.

#### 2.3.4.2 Cohort definition (prescription drug-user and misuse cohorts)

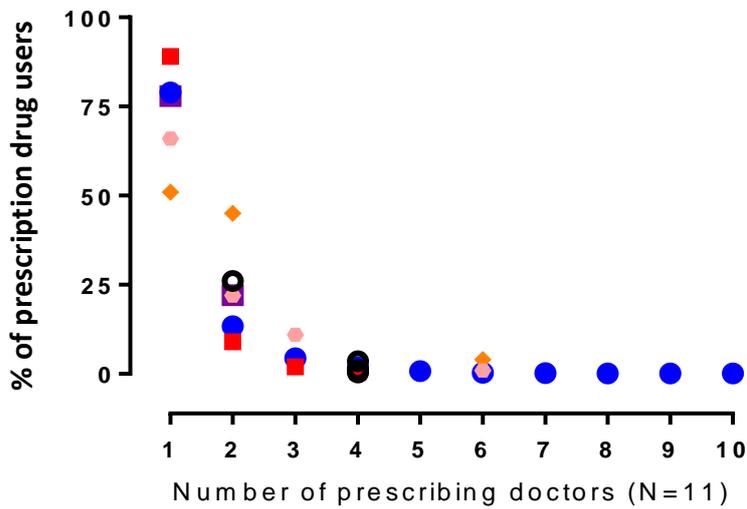
Misuse was measured more frequently in drug-user cohorts (87 instances) than misuse cohorts (33 instances). The extent of misuse was most commonly  $\leq 10\%$  for drug-users (58 instances, 66.7%) and  $\geq 20\%$  in misuse cohorts (23 instances, 69.7%). However, the extent of misuse ranged considerably between drug-user (0.01–63.2%) and misuse (0.2–93.5%) cohorts, reflecting the variation in the measures and thresholds utilised, and the cohort definition. A strict cohort definition increased the reported extent of misuse; misuse cohorts had stricter cohort definitions than drug-user cohorts. In general, for drug-user cohorts a high reported extent of misuse reflected a low threshold for misuse, and for misuse cohorts the higher the reported extent of misuse, the stricter the cohort definition.

#### 2.3.4.3 Time period of assessment

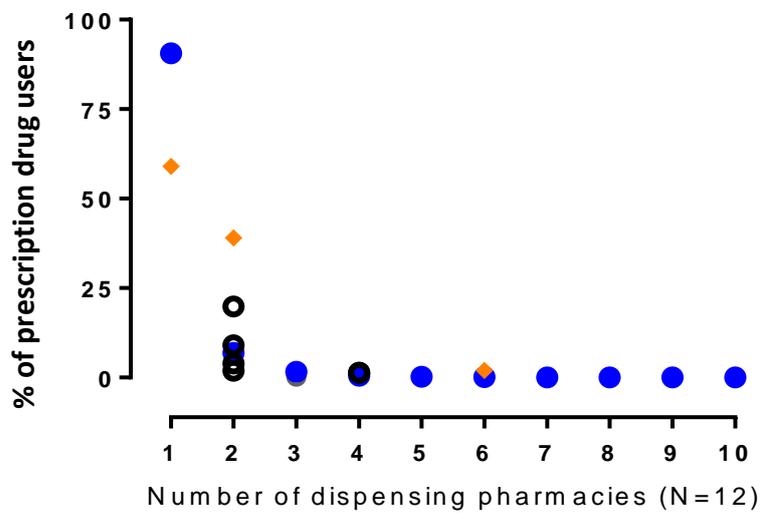
Measures of misuse were assessed from 7 days to 4 years. The most commonly investigated time period was 12 months, utilised in 44% of instances of reporting misuse. Due to the heterogeneity of thresholds of misuse and cohort definitions, we were unable to make any further observations concerning the time period of assessment.

**Figure 2.2** Variation in prevalence of prescription drug access and misuse according to thresholds

**2.2A**



**2.2B**



- Bramness 2007
- ◆ Han
- Katz
- Thirion
- Wilsey 2011
- Study reported a single measure of prescription drug use

### *2.3.5 Factors associated with prescription drug misuse*

Fifteen studies investigated variations in the extent of misuse based on drug class (four studies), specific drug(s) (12 studies) and/or formulation(s) of interest (three studies) (SM 9).

Four studies compared the extent of misuse across different drug classes based on the same measure of misuse within each study and found opioid misuse was higher than benzodiazepine misuse (no statistical comparisons were performed).<sup>36–39</sup>

Six studies compared the extent of misuse for two or more drugs in the same class. In the opioid class, oxycodone (compared with tapentadol) and methadone (compared with morphine, oxycodone, fentanyl and hydrocodone) had a significantly higher risk of misuse-related behaviour.<sup>40,41</sup> Within the benzodiazepine class, three studies demonstrated that flunitrazepam had the highest extent of misuse compared with several other benzodiazepines.<sup>42,43</sup> Within the antidepressant class, tianeptine (compared with mianserin) had the highest extent of misuse.<sup>44</sup> However, no statistical comparisons were performed in the benzodiazepine or antidepressant studies.

Three studies explored the influence of the drug formulation on the extent of misuse. A larger proportion of stronger benzodiazepines<sup>42</sup> and short-acting opioids<sup>45</sup> were dispensed to the misuse cohort compared with weaker or long-acting counterparts, respectively.

### *2.3.6 Justification of measures of misuse*

Thirty-four studies reported a basic rationale for at least one measure of misuse by either citing previously published work (24 studies), mostly their own; using recommendations of

an expert panel (six studies); and/or via empirical analysis (14 studies). Ten studies utilised more than one method of justification. Eighteen studies (34.6%) did not report a rationale for their choice of measure of misuse.

### *2.3.7 Comprehensiveness of reporting observational studies*

The median STROBE score was 27 (range: 19–33; IQR: 23–29) out of a possible 36. Many studies did not report basic cohort details, including sex (20 studies), age (18) and/or cohort size (8). Studies did not identify how they managed any bias (26), loss to follow up (39), missing data (39) or sensitivity analyses (38). Furthermore, 21 studies did not report the funding source.

Forty studies were published from 2008, after the STROBE statement was published; the median STROBE score was 25.5 (range: 19–31; IQR: 22–30) for studies published prior to the STROBE statement, and 27 (range: 19–33; IQR: 24–29) for studies published after the STROBE statement.

## **2.4 Discussion**

Our systematic review synthesised the global literature quantifying prescription drug misuse based on population-level, routinely collected data. Our aim was to examine the measures, extent and factors associated with prescription drug misuse. We found a high level of consistency in the behaviours measuring misuse across the 52 studies, reflecting common jurisdictional data holdings and the limited number of variables with the capacity to investigate misuse behaviour in routine data collections. However, due to the heterogeneity in thresholds of misuse, cohort definitions and time period of assessment, we were unable

to make definitive comparisons regarding the extent or factors associated with misuse across time or healthcare settings. Despite this significant limitation in the current literature, going forward, the international research community has the capacity to make significant and timely inroads in this field by developing and harmonising minimum reporting standards for a core set of pre-defined metrics. Our review and recommendations are timely and highly pertinent to the recent FDA call for submissions regarding the post-market surveillance of specific prescription opioids.<sup>24</sup>

The harms associated with prescription drug misuse, particularly opioid misuse, have now reached epidemic proportions in many jurisdictions internationally.<sup>46,47</sup> Despite the escalation in prescription drug use and consequences of misuse,<sup>8,48,49</sup> we have limited knowledge about the extent of, and variations in, population-level misuse globally. We propose that a comprehensive and harmonised evidence-base, underpinned by routinely collected data, monitoring the extent of prescription drug misuse, will add significant value to the global effort in quantifying this problem. Moreover, this effort will enhance our understanding of the impact of policy responses attempting to address this problem.

The use of dispensing claims for post-market drug surveillance is a cost effective means of monitoring longitudinal, population-level prescription drug use and misuse. Many regulatory and funding agencies use dispensing claims to monitor prescription drug use, misuse and/or diversion.<sup>23</sup> In this review, we demonstrate routine dispensing data are used increasingly in peer-reviewed literature to explore prescription drug misuse, with over 60% of reviewed studies published since 2010. Findings from population-level, routinely collected dispensing/prescription data have the capacity to complement other methodological

approaches, such as detailed medical record reviews, surveys and in-depth qualitative studies, to enhance our understanding of prescription drug misuse. Moreover, linking dispensing claims with other routinely collected health data, such as hospitalisations and vital status will also provide further insight into the risk factors and drug access patterns related to harm.

Our review has several limitations. It is not certain that all relevant studies were captured. Over 10,000 abstracts were reviewed and despite employing a comprehensive search strategy to identify relevant articles;<sup>50</sup> 14 studies were identified through back references, Scopus citations or Google Scholar searches, indicating the challenges of targeted searching and the diversity of keywords and subject headings used across studies. Articles that were not published in English were excluded; as nearly half of the included studies originated from Europe, we may have missed studies published in other languages.<sup>51,52</sup> Our estimates of prescription drug misuse are solely from the perspective of the healthcare payer; we are unable to address access issues outside the dispensing episodes observed in the data including drugs obtained illegally. The STROBE guidelines were applied to all studies, irrespective of publication date. However, the results did not vary considerably for studies published prior to or post STROBE statement publication. A search of journal contents was not undertaken due to the diversity of journals where the studies were published (32 unique journals published the 52 reviewed studies).<sup>52</sup> These limitations do not impact our key findings. In fact, adding more studies is likely to contribute further to the heterogeneity we found across the field. Studies and metrics were categorised to synthesise the disparate literature. For example, misuse measures were categorised as stand-alone or composite measures. All measures based on a single metric (e.g.  $\geq 4$  prescribers in 6 months) applied to

a previously identified misuse cohort (e.g.  $\geq 4$  dispensing pharmacies in 6 months) were categorised as composite measures. These occurrences could have been categorised as stand-alone measures; however, this choice impacts on data presentation, not key findings. Finally, a key limitation of the literature is the notable absence of validation to establish whether the proxies actually measure misuse or are associated with harm.<sup>23</sup>

Despite these limitations, this is one of the most comprehensive systematic reviews of this field to date. Our review was highly focused on measuring prescription drug misuse in routinely collected data. Other published reviews focused on jurisdiction-specific literature,<sup>23,47,53–56</sup> self-report or medical chart data to ascertain use,<sup>47,55–57</sup> specific drug classes<sup>23,53,54,57</sup> or patient populations.<sup>54–57</sup> The interpretation of these reviews were also impeded by the heterogeneity in study design<sup>54,56</sup> and/or methods.<sup>47,54–56</sup> However, the authors of these reviews did not suggest any practical solutions for unifying research in the field. Our recommendations provide a foundation that will increase the dialogue between researchers and unify future routine monitoring and post-market surveillance research (see section 2.4.1 *Reporting recommendations*). Our study complements two recent comprehensive reviews; one examining the patient, prescriber and environmental characteristics associated with opioid-related death,<sup>54</sup> and the other an overview by FDA researchers of the appropriateness of US data sources for measuring prescription opioid abuse.<sup>23</sup>

#### *2.4.1 Reporting recommendations*

We have developed recommendations to harmonise the measurement and reporting of prescription drug misuse in routine data collections. These recommendations were not part

of the original study objectives; instead they are underpinned by our learning in this review, particularly the challenges we faced in identifying studies and comparing the extent of misuse across studies (Box 2.2). Our recommendations centre around three key areas: methodology (promotion of consistent metrics to determine appropriate measures of misuse), reporting (listing all drugs by generic name included in each study and the specifics of the misuse measures) and study nomenclature (where possible, consistency in the use of keywords including 'prescription drug misuse', that facilitate direct mapping to searchable subject headings). Future studies should combine these recommendations with the current standard reporting requirements for observational studies,<sup>26,27</sup> which will support the current FDA initiative and add value across other jurisdictions.

## ***2.5 Conclusions***

Prescription drug misuse has reached epidemic proportions in the US and is fast increasing in other jurisdictions. Despite the consistency in data holdings and metrics used to define misuse in routine data collections we found considerable variation in measures of prescription drug misuse, cohort definitions and time period of assessment. The adoption and modification of policies targeting prescription drug misuse are easier to argue for, or against, when the impacts are measured robustly and reproducible effects have been demonstrated across multiple settings. Thus, having consistent metrics for prescription drug misuse across jurisdictions is a very simple step, but one with potentially far-reaching consequences.

**Box 2.2** Recommendations for observational studies investigating prescription drug misuse

We recommend researchers should state explicitly the following issues in each published manuscript:

*Methodology*

1. Detail the distribution of the metric(s) and the rationale for the threshold(s) for misuse

*Reporting*

2. List the generic name of all prescription drugs studied
3. Detail cohort characteristics for every analysis undertaken
4. Identify all metrics (variables) and thresholds used to measure misuse
5. State the time period in which the metric(s) is measured (we recommend that studies should report misuse over at least a 6-month period)
6. When using a composite measure of misuse, report the extent of misuse for each component and the composite

*Study identification*

7. Use 'prescription drug misuse' as a keyword or subject heading

*Study terminology*

## 2.6 References

1. Barrett SP, Meisner JR, Stewart SH. What constitutes prescription drug misuse? Problems and pitfalls of current conceptualizations. *Curr Drug Abuse Rev.* 2008; 1(3): 255–262.
2. Nolan W, Gannon R. Combating the increase in opioid misuse. *Conn Med.* 2013; 77(8): 495–498.
3. Bartley J, Watkins LR. Comment on: excessive opioid use and the development of chronic migraine. *Pain.* 2009; 145(1–2): 262–263.
4. Baandrup L, Allerup P, Lublin H, Nordentoft M, Peacock L, et al. Evaluation of a multifaceted intervention to limit excessive antipsychotic co-prescribing in schizophrenia out-patients. *Acta Psychiatr Scand.* 2010; 122(5): 367–374.
5. Petersen AB, Andersen SE, Christensen M, Larsen HL. Adverse effects associated with high-dose olanzapine therapy in patients admitted to inpatient psychiatric care. *Clin Toxicol (Phila).* 2014; 52(1): 39–43.
6. Huston B, Mills K, Froloff V, McGee M. Bladder rupture after intentional medication overdose. *Am J Forensic Med Pathol.* 2012; 33(2): 184–185.
7. Garland EL, Froeliger B, Zeidan F, Partin K, Howard MO. The downward spiral of chronic pain, prescription opioid misuse, and addiction: cognitive, affective, and neuropsychopharmacologic pathways. *Neurosci Biobehav Rev.* 2013; 37(10 Pt 2): 2597–2607.
8. Gomes T, Mamdani MM, Dhalla IA, Paterson J, Juurlink DN. Opioid dose and drug-related mortality in patients with non-malignant pain. *Arch Intern Med.* 2011; 171(7): 686–691.

9. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, et al. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med.* 2012; 13(1): 87–95.
10. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med.* 2010; 152(2): 85–92.
11. Paulozzi LJ. Prescription drug overdoses: a review. *J Saf Res.* 2012; 43(4): 283–9.
12. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA.* 2013; 309(7): 657–659.
13. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA.* 2008; 300(22): 2613–2620.
14. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. *Drug Alcohol Depend.* 2012; 125(1–2): 8–18.
15. Gudín JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. *Postgrad Med.* 2013; 125(4): 115–130.
16. Nuckols TK, Anderson L, Popescu I, Diamant AL, Doyle B, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med.* 2014; 160(1): 38–47.
17. Braker LS, Reese AE, Card RO, Van Howe RS. Screening for potential prescription opioid misuse in a Michigan Medicaid population. *Fam Med.* 2009; 41(10): 729–734.
18. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: summary of national findings. NSDUH series H-46, HHS publication no. (SMA) 13-4795, 2013. Available at:

<http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm#ch2>. Accessed 1 May 2015.

19. Merlo LJ, Singhakant S, Cummings SM, Cottler LB. Reasons for misuse of prescription medication among physicians undergoing monitoring by a physician health program. *J Addict Med*. 2013; 7(5): 349–353.
20. Fulton HG, Barrett SP, Stewart SH, Maclsaac C. Prescription opioid misuse: characteristics of earliest and most recent memory of hydromorphone use. *J Addict Med*. 2012; 6(2): 137–144.
21. McCall KL III, Tu C, Lacroix M, Holt C, Wallace KL, et al. Controlled substance prescribing trends and physician and pharmacy utilization patterns: epidemiological analysis of the Maine prescription monitoring program from 2006 to 2010. *J Subst Use*. 2013; 18(6): 467–475.
22. Hernandez SH, Nelson LS. Prescription drug abuse: insight into the epidemic. *Clin Pharmacol Ther*. 2010; 88(3): 307–17.
23. Secora AM, Dormitzer CM, Staffa JA, Dal Pan GJ. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiol Drug Saf*. 2014; 23(12): 1227–1237.
24. US Department of Health & Human Services. Postmarketing requirements for the class-wide extended-release/long-acting opioid analgesics. 2014. Available at: <http://www.fda.gov/drugs/newsevents/ucm384489.htm>. Accessed 30 June 2014.
25. Carnahan RM, Moores KG. Mini-Sentinel’s systematic reviews of validated methods for identifying health outcomes using administrative and claims data: methods and lessons learned. *Pharmacoepidemiol Drug Saf*. 2012; 21(Suppl 1): 82–89.

26. von Elm EMD, Altman DGD, Egger MMD, Pocock SJ, Gotsche PC, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Prev Med.* 2007; 45(4): 247-251.
27. Vandembroucke JP, von Elm E, Altman DG, Gotsche PC, Mulrow CD, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiol.* 2007; 18(6): 805–835.
28. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, et al. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend.* 2003; 69(3): 215–232.
29. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick R. Definitions related to the use of pharmaceutical opioids: extramedical use, diversion, non-adherence and aberrant medication-related behaviours. *Drug Alcohol Rev.* 2011; 30(3): 236–245.
30. Smith SM, Dart RC, Katz NP, Paillard F, Adams EH, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTION systematic review and recommendations. *Pain.* 2013; 154(11): 2287–2296.
31. Katz N, Panas L, Kim M, Audet AD, Bilanksy A, et al. Usefulness of prescription monitoring programs for surveillance: analysis of Schedule II opioid prescription data in Massachusetts, 1996–2006. *Pharmacoepidemiol Drug Saf.* 2010; 19(2): 115–123.
32. Logan J, Liu Y, Paulozzi L, Zhang K, Jones C. Opioid prescribing in emergency departments: the prevalence of potentially inappropriate prescribing and misuse. *Med Care.* 2013; 51(8): 646–653.

33. Pearson SA, Soumerai S, Mah C, Zhang F, Simoni-Wastila L, et al. Racial disparities in access after regulatory surveillance of benzodiazepines. *Arch Intern Med.* 2006; 166(5): 572–579.
34. Peirce GL, Smith MJ, Abate MA, Halverson J. Doctor and pharmacy shopping for controlled substances. *Med Care.* 2012; 50(6): 494–500.
35. Bachs LC, Bramness JG, Engeland A, Skurtveit S. Repeated dispensing of codeine is associated with high consumption of benzodiazepines. *Nor Epidemiol.* 2008; 18(2): 185–190.
36. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Assessing opioid shopping behavior: a large cohort study from a medication dispensing database in the US. *Drug Saf.* 2012; 35(4): 325–334.
37. Dormuth CR, Miller TA, Huang A, Mamdani MM, Juurlink DN. Effect of a centralized prescription network on inappropriate prescriptions for opioid analgesics and benzodiazepines. *CMAJ.* 2012; 184(16): E852-E856.
38. Wilsey BL, Fishman SM, Gilson AM, Casamalhuapa C, Baxi H, et al. Profiling multiple provider prescribing of opioids, benzodiazepines, stimulants, and anorectics. *Drug Alcohol Depend.* 2010; 112(1–2): 99–106.
39. Pauly V, Pradel V, Pourcel L, Nordmann S, Frauger E, et al. Estimated magnitude of diversion and abuse of opioids relative to benzodiazepines in France. *Drug Alcohol Depend.* 2012; 126(1–2): 13–20.
40. Cepeda MS, Fife D, Vo L, Mastrogiovanni G, Yuan Y. Comparison of opioid doctor shopping for tapentadol and oxycodone: a cohort study. *J Pain.* 2013; 14(2): 158–164.

41. Wilsey BL, Fishman SM, Gilson AM, Casamalhuapa C, Baxi H, et al. An analysis of the number of multiple prescribers for opioids utilizing data from the California Prescription Monitoring Program. *Pharmacoepidemiol Drug Saf.* 2011; 20(12): 1262–1268.
42. Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using ‘doctor shopping’ as an indicator. *CNS Drugs.* 2010; 24(7): 611–620.
43. Pauly V, Frauger E, Pradel V, Nordmann S, Pourcel L, et al. Monitoring of benzodiazepine diversion using a multi-indicator approach. *Int Clin Psychopharmacol.* 2011; 26(5): 268–277.
44. Rouby F, Pradel V, Frauger E, Pauly V, Natali F, et al. Assessment of abuse of tianeptine from a reimbursement database using ‘doctor-shopping’ as an indicator. *Fundam Clin Pharmacol.* 2012; 26(2): 286–294.
45. Gilson AM, Fishman SM, Wilsey BL, Casamalhuapa C, Baxi H. Time series analysis of California’s prescription monitoring program: impact on prescribing and multiple provider episodes. *J Pain.* 2012; 13(2): 103–111.
46. McCarthy M. Prescription drug abuse up sharply in the USA. *Lancet.* 2007; 369(9572): 1505–1506.
47. Casati A, Sedefov R, Pfeiffer-Gerschel T. Misuse of medicines in the European Union: a systematic review of the literature. *Eur Addict Res.* 2012; 18(5): 228–245.
48. Blanch B, Pearson S, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *Br J Clin Pharmacol.* 2014; 78(5): 1159–1166.

49. Unick GJ, Rosenblum D, Mars S, Ciccarone D. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993–2009. *PLoS One*. 2013; 8(2): e54496.
50. Hoffmann T, Erueti C, Thorning S, Glasziou P. The scatter of research: cross sectional comparison of randomised trials and systematic reviews across specialties. *BMJ*. 2012; 344: e3223.
51. Martin-Latry K, Begaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! *Pharmacoepidemiol Drug Saf*. 2010; 19(3): 256–265.
52. Glasziou P. Systematic reviews in health care: a practical guide. Cambridge: Cambridge University Press; 2001.
53. Fischer B, Argento E. Prescription opioid related misuse, harms, diversion and interventions in Canada: a review. *Pain Physician*. 2012; 15(3 Suppl): ES191–ES203.
54. King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990–2013: a systematic review. *Am J Public Health*. 2014; 104(8): e32–e42.
55. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain*. 2008; 24(6): 497–508.
56. Young AM, Glover N, Havens JR. Nonmedical use of prescription medications among adolescents in the United States: a systematic review. *J Adolesc Health*. 2012; 51(1): 6–17.
57. Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, et al. Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry*. 2008; 47(1): 21–31.

58. Bellanger L, Vigneau C, Pivette J, Jolliet P, Sebille V. Discrimination of psychotropic drugs over-consumers using a threshold exceedance based approach. *Stat Anal Data Min.* 2013; 6(2): 91–101.
59. Bramness JG, Furu K, Engeland A, Skurtveit S. Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol.* 2007; 64(2): 210–218.
60. Gjerden P, Bramness JG, Slørdal L. The use and potential abuse of anticholinergic antiparkinson drugs in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol.* 2009; 67(2): 228–233.
61. Wainstein L, Victorri-Vigneau C, Sebille V, Hardouin JB, Feuillet F, et al. Pharmacoepidemiological characterization of psychotropic drugs consumption using a latent class analysis. *Int Clin Psychopharmacol.* 2011; 26(1): 54–62.
62. White AG, Birnbaum HG, Schiller M, Tang J, Katz NP. Analytic models to identify patients at risk for prescription opioid abuse. *Am J Manag Care.* 2009; 15(12): 897–906.
63. Parente ST, Kim SS, Finch MD, Schloff LA, Rector TS, et al. Identifying controlled substance patterns of utilization requiring evaluation using administrative claims data. *Am J Manag Care.* 2004; 10(11 Pt 1): 783–790.
64. Victorri-Vigneau C, Feuillet F, Wainstein L, Grall-Bronnec M, Pivette J, et al. Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. *Eur J Clin Pharmacol.* 2013; 69(11): 1965–1972.
65. Cepeda MS, Fife D, Berlin JA, Mastrogiovanni G, Yuan Y. Characteristics of prescribers whose patients shop for opioids: results from a cohort study. *J Opioid Manag.* 2012; 8(5): 285–291.

66. Martin BC, Fan M-Y, Edlund MJ, Devries A, Braden JB, et al. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med.* 2011; 26(12): 1450–1457.
67. Sullivan MD, Edlund MJ, Fan M-Y, Devries A, Brennan Braden J, et al. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and Medicaid insurance plans: the TROUP Study. *Pain.* 2010; 150(2): 332–339.
68. Nordmann S, Pradel V, Lapeyre-Mestre M, Frauger E, Pauly V, et al. Doctor shopping reveals geographical variations in opioid abuse. *Pain Physician.* 2013; 16(1): 89–100.
69. Pauly V, Frauger E, Pradel V, Rouby F, Berbis J, et al. Which indicators can public health authorities use to monitor prescription drug abuse and evaluate the impact of regulatory measures? Controlling high dosage buprenorphine abuse. *Drug Alcohol Depend.* 2011; 113(1): 29–36.
70. Pradel V, Frauger E, Thirion X, Ronfle E, Lapierre V, et al. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. *Pharmacoepidemiol Drug Saf.* 2009; 18(1): 36–43.
71. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, et al. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. *Pharmacoepidemiol Drug Saf.* 2004; 13(7): 473–481.
72. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Opioid shopping behavior: how often, how soon, which drugs, and what payment method. *J Clin Pharmacol.* 2013; 53(1): 112–117.

73. Frauger E, Pauly V, Thirion X, Natali F, Pradel V, et al. Estimation of clonazepam abuse liability: a new method using a reimbursed drug database. *Int Clin Psychopharmacol*. 2009; 24(6): 318–324.
74. Frauger E, Pauly V, Natali F, Pradel V, Reggio P, et al. Patterns of methylphenidate use and assessment of its abuse and diversion in two French administrative areas using a proxy of deviant behavior determined from a reimbursement database: main trends from 2005 to 2008. *CNS Drugs*. 2011; 25(5): 415–424.
75. Cepeda MS, Fife D, Yuan Y, Mastrogiovanni G. Distance travelled and frequency of interstate opioid dispensing in opioid shoppers and nonshoppers. *J Pain*. 2013; 14(10): 1158–1161.
76. Hoffman L, Enders JL, Pippins J, Segal R. Reducing claims for prescription drugs with a high potential for abuse. *Am J Health Syst Pharm*. 2003; 60(4): 371–374.
77. Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? *Pain*. 2011; 152(7): 1555–1561.
78. Thirion X, Lapierre V, Micallef J, Ronfle E, Masut A, et al. Buprenorphine prescription by general practitioners in a French region. *Drug Alcohol Depend*. 2002; 65(2): 197–204.
79. Goodman FDC, Glassman P. Evaluating potentially aberrant outpatient prescriptions for extended-release oxycodone. *Am J Health Syst Pharm*. 2005; 62(24): 2604–2608.
80. Mailloux AT, Cummings SW, Mugdh M. A decision support tool for identifying abuse of controlled substances by ForwardHealth Medicaid members. *J Hosp Mark Public Relations*. 2010; 20(1): 34–55.

81. Ross-Degnan D, Simoni-Wastila L, Brown JS, Gao X, Mah C, et al. A controlled study of the effects of state surveillance on indicators of problematic and non-problematic benzodiazepine use in a Medicaid population. *Int J Psychiatry Med.* 2004; 34(2): 103–123.
82. Victorri-Vigneau C, Sebillé V, Gerardin M, Simon D, Pivette J, et al. Epidemiological characterization of drug overconsumption: the example of antidepressants. *J Addict Dis.* 2011; 30(4): 342–350.
83. Soumerai SB, Simoni-Wastila L, Singer C, Mah C, Gao X, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv.* 2003; 54(7): 1006–1011.
84. Simoni-Wastila L, Ross-Degnan D, Mah C, Gao X, Brown J, et al. A retrospective data analysis of the impact of the New York triplicate prescription program on benzodiazepine use in Medicaid patients with chronic psychiatric and neurologic disorders. *Clin Ther.* 2004; 26(2): 322–336.
85. Bramness JG, Rossow I. Can the total consumption of a medicinal drug be used as an indicator of excessive use? The case of carisoprodol. *Drugs Edu Prev Policy.* 2010; 17(2): 168–180.
86. Fredheim OMS, Skurtveit S, Moroz A, Breivik H, Borchgrevink PC. Prescription pattern of codeine for non-malignant pain: a pharmacoepidemiological study from the Norwegian Prescription Database. *Acta Anaesthesiol Scand.* 2009; 53(5): 627–633.
87. Hartz I, Tverdal A, Skurtveit S. Social inequalities in use of potentially addictive drugs in Norway: use among disability pensioners. *Nor Epidemiol.* 2009; 19(2): 209–218.

88. Victorri-Vigneau C, Basset G, Jolliet P. How a novel programme for increasing awareness of health professionals resulted in a 14% decrease in patients using excessive doses of psychotropic drugs in western France. *Eur J Clin Pharmacol*. 2006; 62(4): 311–316.
89. Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan [published erratum appears in *JAMA*. 2012;307(23):2489]. *JAMA*. 2012; 307(9): 940–947.
90. Rice JB, White AG, Birnbaum HG, Schiller M, Brown DA, Roland CL. A model to identify patients at risk for prescription opioid abuse, dependence, and misuse. *Pain Med*. 2012; 13(9): 1162–1173.
91. McDonald DC, Carlson KE. Estimating the prevalence of opioid diversion by “doctor shoppers” in the United States. *PLoS One*. 2013; 8(7): e69241.

### ***Chapter Three: An overview of the patterns of prescription opioid use, costs and related harms in Australia***

Prescription opioid use and associated harms have increased to concerning levels in many jurisdictions, particularly in the US and Canada. Therefore, it is not surprising that in our systematic review, opioid analgesics are the most commonly investigated drug class in relation to potential misuse. Several Australian studies have demonstrated increases in opioid use or harms for specific opioids, such as oxycodone and fentanyl, with a focus on specific Australian States. However, no Australian studies have quantified national opioid use and opioid-related harms for all PBS-listed opioids.

In this chapter we present an ecological study examining three national, routinely collected, publically available datasets (pharmaceutical claims, hospitalisation claims and cause of death data) to examine national prescription opioid use and related harms over 20 years.

This chapter is a reproduction of the following publication:

Bianca Blanch, Sallie-Anne Pearson, Paul S. Haber. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *British Journal of Clinical Pharmacology*. 2014; 78(5): 1159-1166.

Formatting note: To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. The key points and

abstract are formatted according to the *British Journal of Clinical Pharmacology* style guide.

We provide the reference list at the end of this chapter.

## **Key Points**

### *What is already known about this subject?*

- Prescribed opioid use is rising, particularly in the US and Canada, to treat cancer and non-cancer pain.
- The consequences of prescribed opioid misuse are increasing, specifically in the US.
- Currently, there is no Australian research demonstrating patterns/consequences of opioid utilisation for all opioids subsidised by the national reimbursement drug scheme.

### *What does this study add?*

- In Australia opioid use is increasing, as is the cost to the government and the personal consequences of opioid use including number of hospitalisations and deaths.
- Further research is required to understand the patterns of prescribed drug use to reduce/prevent associated adverse consequences.

## ***Abstract***

### *Objective*

To report Australian population trends in subsidised prescribed opioid use, total costs to the Australian government to subsidise these drugs and opioid-related harms based on hospitalisations and accidental poisoning deaths.

### *Methods*

We utilised three national aggregated data sources including dispensing claims from the Pharmaceutical Benefits Scheme, opioid-related hospitalisations from the National Hospital Morbidity Database and accidental poisoning deaths from the Australian Bureau of Statistics.

### *Results*

Between 1992 and 2012, opioid dispensing episodes increased 15-fold (500 000 to 7.5 million) and the corresponding cost to the Australian government increased 32-fold (\$8.5 million to \$271 million). Opioid-related harms also increased. Prescription opioid-related hospitalisations increased from 605 to 1464 cases (1998–2009), outnumbering hospitalisations due to heroin poisonings since 2001. Deaths due to accidental poisoning (pharmaceutical opioids and illicit substances combined) increased from 151 to 266 (2002–2011), resulting in a rise in the death rate of 0.78 to 1.19 deaths/100 000 population over 10 years. Death rates increased 1.8 fold in males and 1.4 fold in females.

## *Conclusions*

The striking increase in opioid use and related harms in Australia is consistent with trends observed in other jurisdictions. Further, there is no evidence to suggest these increases are plateauing. There is currently limited evidence in Australia about individual patterns of opioid use and the associated risk of adverse events. Further research should focus on these important issues so as to provide important evidence supporting effective change in policy and practice.

### **3.1 Introduction**

There has been a long-standing role for opioid analgesics to treat patients with cancer pain. Over the past 20 years, the indication for opioids has expanded to treat acute and chronic, non-cancer pain. Opioids have been shown to be effective for short term pain relief but there is only limited evidence of the long term benefits of opioid use for any indication.<sup>1,2</sup> As a consequence of extending these indications, opioid utilisation has increased significantly in many jurisdictions, most notably in the US.<sup>3-7</sup> Increased use, coupled with prolonged use in patients with chronic non-cancer pain, have led to concerns on the part of policy makers, health professionals and the general public about population and individual risks and benefits of prescribed opioids.<sup>8,9</sup>

Three professional bodies from the US and Australia have outlined concerns about the staggering increases in opioid use and the increase in related harms. However, they caution against strict regulations in accessing these prescription drugs for patients requiring pain relief.<sup>8-10</sup>

There has been an increase in opioid use in Australia over the past 30 years.<sup>11-18</sup> In 2013, there were 241 preparations for 12 opioid analgesics available for prescribing in Australia. Morphine (87 preparations), tramadol (48 preparations), fentanyl (43 preparations) and oxycodone (37 preparations) have the highest number of preparations (Table 3.1). Eight opioids are currently subsidised by the Pharmaceutical Benefit Scheme (PBS): buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone and tramadol. As of December 2013, four opioids are available for prescription in Australia, but are not PBS-listed; alfentanil, dextropropoxyphene, pethidine and tapentadol.

**Table 3.1** The number of opioids available in Australia for prescription

Opioids available in Australia for prescription	Number of opioid preparations available in Australia <sup>a</sup> for analgesia	Number of opioid preparations available in Australia <sup>a</sup> to treat opiate maintenance therapy
Alfentanil	2	0
Buprenorphine	5	5
Codeine	2	0
Dextropropoxyphene	1	0
Fentanyl	43	0
Hydromorphone	5	0
Methadone	2	5
Morphine	87	0
Oxycodone	37	0
Pethidine	4	0
Tapentadol	5	0
Tramadol	48	0
<b>TOTAL</b>	<b>241</b>	<b>10</b>

<sup>a</sup> A preparation is defined as an entry in the 'narcotic analgesics' section of MIMS regardless of PBS status, pack size and preparation. This reflects the product range available to prescriber and consumer (MIMS data accessed 27 September 2013).

In Australia, studies have investigated the harms related to the use of specific opioids such as oxycodone, fentanyl and morphine.<sup>14,15,18</sup> This paper updates our previous report<sup>11</sup> on trends in PBS-subsidised opioid use in Australia. We also report the total costs to the Australian government to subsidise these prescription drugs. Lastly, we report the opioid-related harms based on hospitalisations and accidental deaths.

## **3.2 Methods**

### *3.2.1 Setting*

In 2012, the population of Australia was approximately 22.7 million. Australia has a publically funded universal healthcare system entitling all citizens and permanent residents to a range of subsidised health services including free treatment in public hospitals and subsidised treatment in private hospitals. It also includes a range of subsidised outpatient services including consultations with clinicians and prescribed drugs. These arrangements place Australia in a unique position to analyse patterns of prescription drug utilisation and reported harms at a population level.

### *3.2.2 Data sources and method*

Three national publically available, online aggregated data sources were utilised to report patterns of PBS-listed opioid utilisation and costs to the government; number of hospitalisations due to opioid poisonings, and number of accidental deaths related to illicit drugs and pharmaceutical opioids.

### *3.2.3 Prescribed opioid use and costs*

The PBS is a national drug reimbursement system subsidising a range of prescribed drugs. PBS dispensing records are available in aggregate (de-identified) form via Medicare Australia (<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>) where data queries can be performed to establish volume and costs of specific PBS-item numbers according to time periods of interest. We report the number of dispensing episodes and cost to the government for the eight PBS-listed opioids by calendar year from 1992 to 2012 inclusive. We do not report volume of combination drugs, nor population-, age- or sex-adjusted data.

There are several limitations associated with PBS data. The dispensing of a PBS drug is not recorded in the database if: the Commonwealth does not contribute to the cost of the drug; it is given within some public hospital settings; or the indication is to treat an opiate maintenance therapy (drugs for this indication are funded by the Section 100 Highly Specialised Drugs Program). Consequently, there is under-ascertainment of PBS-listed drugs that fall below the general beneficiary copayment. In 2013, 78 of the 146 PBS item numbers related to an opioid preparation were priced under the general beneficiary copayment of AU\$36.10. It is not possible to report the number of opioids priced under the copayment per year so we cannot determine the extent to which the data presented underestimates total use. We cannot determine the indication for opioid use (i.e. cancer or non-cancer pain), as the same PBS-item number is used for both indications. We excluded opioids that are listed on the Pharmaceutical Benefits Scheme for the indication of palliative care exclusively including fentanyl lozenges (PBS item numbers: 5401G, 5402H, 5404J, 5404K, 5405L, 5406M, 5407N, 5408P, 5409Q, 5410R, 5411T, 5412W).

### *3.2.4 Opioid-related hospitalisations*

The National Hospital Morbidity Database (NHMD) reports hospitalisations in Australia, since July 1993. In this context, a hospitalisation refers to the completion of treatment for an admitted patient due to death, discharge or transfer to another facility. Each hospitalisation is coded according to the International Classification of Diseases (ICD). We report the number of hospitalisations for any opioid-related poisoning, either prescribed or illicit, by financial year (from July 1 to June 30) from 1998 to 2009 inclusive, hereafter referred to as year. These are coded according to the ICD and related health problems, 10th revision, Australian modification (ICD-10-AM).<sup>19</sup> In 1998 the codes across Australian jurisdictions changed to ICD-10 codes, to ensure the reported data are consistent and comparable, therefore we chose to limit the date range. We present the hospitalisations where the ICD-codes indicate the principal diagnosis as a poisoning due to ‘other opioids’ (T40.2) (includes morphine, oxycodone and codeine), methadone (T40.3) and ‘other and unspecified narcotics’ (T40.6). We also present heroin-related (T40.1) hospitalisations to track changes over time. The total number of opioid-related poisonings reported are the sum of hospitalisations using these ICD-10 codes only.<sup>20,21</sup>

The NHMD is a national dataset compiled from data supplied by the State and Territory health authorities. However, one Australian state (South Australia) did not contribute to the data from 1999 to 2001 inclusive. Over-the-counter and prescription codeine preparations may contribute to the ‘other opioids’ poisoning category as the database does not differentiate between these preparations. The NHMD relies on individual coders at each hospital to enter data accurately and consistently regarding principal diagnosis, which is of a high standard in Australia.<sup>22</sup> Hospital data are likely to under-ascertain the true number of

pharmaceutical opioid-related poisonings as they may not be recognised or accurately recorded by clinicians, and hospital coders may under-detect such diagnoses.

### *3.2.5 Accidental poisoning deaths*

Cause of death data were obtained from the Australian Bureau of Statistics (ABS), Causes of Death, 2011 report.<sup>23</sup> The cause of death included in this report is 'accidental poisoning by and exposure to narcotics and hallucinogens not elsewhere classified' (ICD-10 code X42). We report the number of deaths for each calendar year from 2002 to 2011 inclusive. We calculated the rate of death based on the number of deaths and ABS reported Australian population per year.

This is a national dataset recording cause of death based on death certificate data. The ICD-10 code X42 excludes deaths with suicidal or homicidal intent, or where the drug dosage is consistent with therapeutic doses. These data record accidental poisoning deaths caused by codeine, pharmaceutical opioids [methadone, morphine and opium (alkaloids)] and non-pharmaceutical drugs (cannabis, cocaine, heroin, lysergide and mescaline). The ABS cause of death coding does not distinguish between pharmaceutical and illicit substances, therefore it is not possible for us to delineate the contribution of each cause of death in the data.

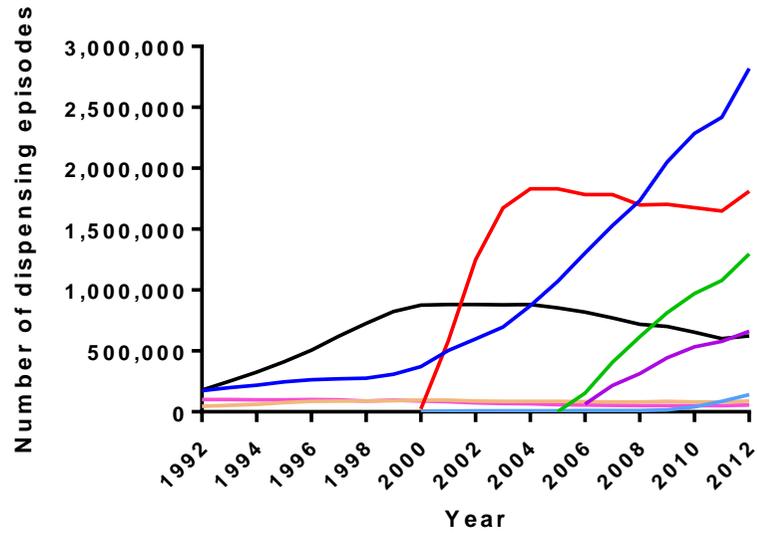
Death certificate data are likely to under-ascertain the true number of pharmaceutical opioid-related poisonings as the cause of death may be attributed to other outcomes such as cardiac arrest or respiratory depression.

### **3.3 Results**

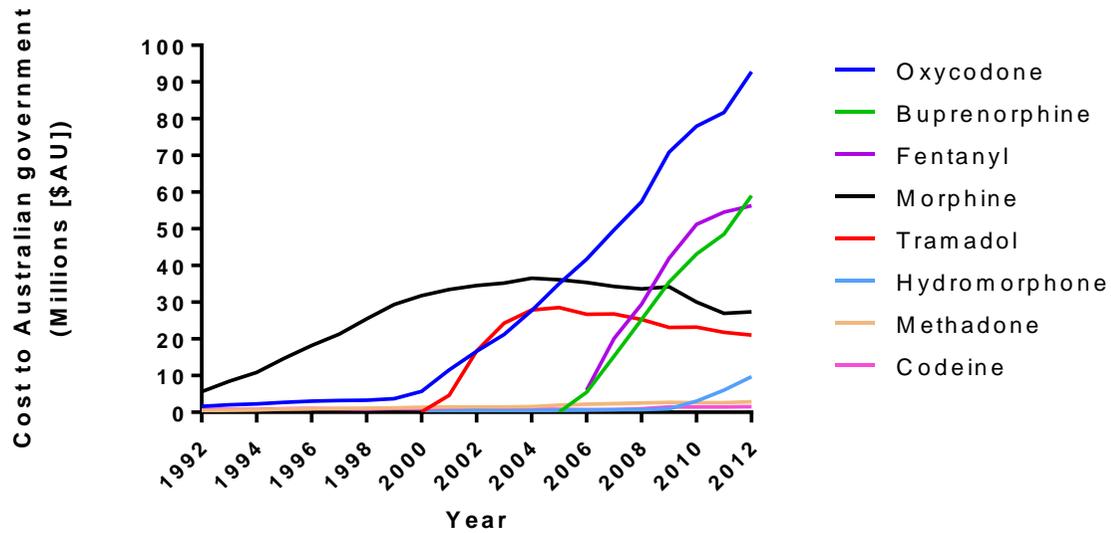
#### *3.3.1 Prescribed opioid use and costs*

Between 1992 and 2012, there was a 15-fold increase in the number of PBS-listed opioid dispensing episodes (500 568 to 7 495 648) (Figure 3.1A). Oxycodone has been the main contributor to the increase in opioid utilisation. The most striking recent trend has been the escalating use of buprenorphine and fentanyl for the treatment of pain. This finding reflects buprenorphine use for the indication of pain only, as data on drugs used to treat opiate maintenance therapy are not available through this data source.

**Figure 3.1A** Number of dispensing episodes for opioid analgesics by medicine in Australia: 1992 – 2012.



**Figure 3.1B** Benefits paid by the Australian government for opioid analgesics in Australia: 1992 – 2012.

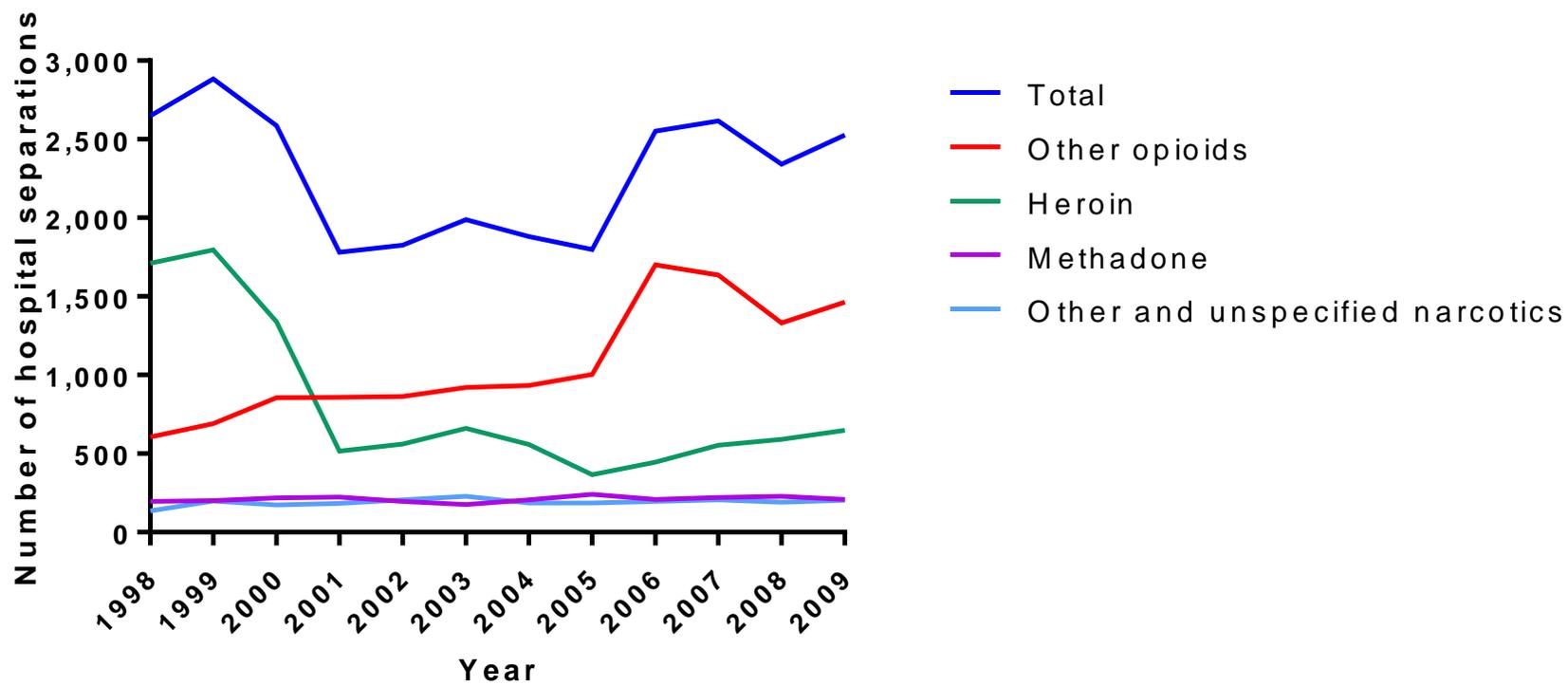


In 1992, the Australian government paid approximately \$8.5 million (for 500 568 dispensing episodes) in subsidies for PBS-listed opioids, increasing to \$270.8 million (for 7.5 million dispensing episodes) in 2012, a 32-fold increase (Figure 3.1B). In 2012, oxycodone preparations accounted for 38% of the total number of dispensing episodes (2.8 million) and 34% of the benefits paid (\$92.7 million). The cost of buprenorphine and fentanyl to the PBS are rising at a striking rate and now rank second and third in terms of opioid-related costs, respectively. Since 2009, the combined annual cost of buprenorphine and fentanyl has exceeded the annual cost of oxycodone.

### *3.3.2 Opioid-related harms*

In 1998, 65% of hospitalisations due to opioid poisoning were attributable to heroin and 23% due to 'other opioids'. In 2001, 'other opioids' overtook heroin as the leading cause of opioid-related hospitalisations; by 2009, 'other opioids' accounted for 58% (Figure 3.2). There was a decline in the total number of opioid poisonings from 1999 to 2002 but since 2005 the number of opioid-related poisonings has increased primarily due to 'other opioids'. Methadone and 'other and unspecified narcotics' hospitalisation numbers have remained stable over this time period.

Figure 3.2 Number of hospitalisations by opioid poisoning type across Australia: 1998 – 2009.



### *3.3.3 Accidental poisoning deaths*

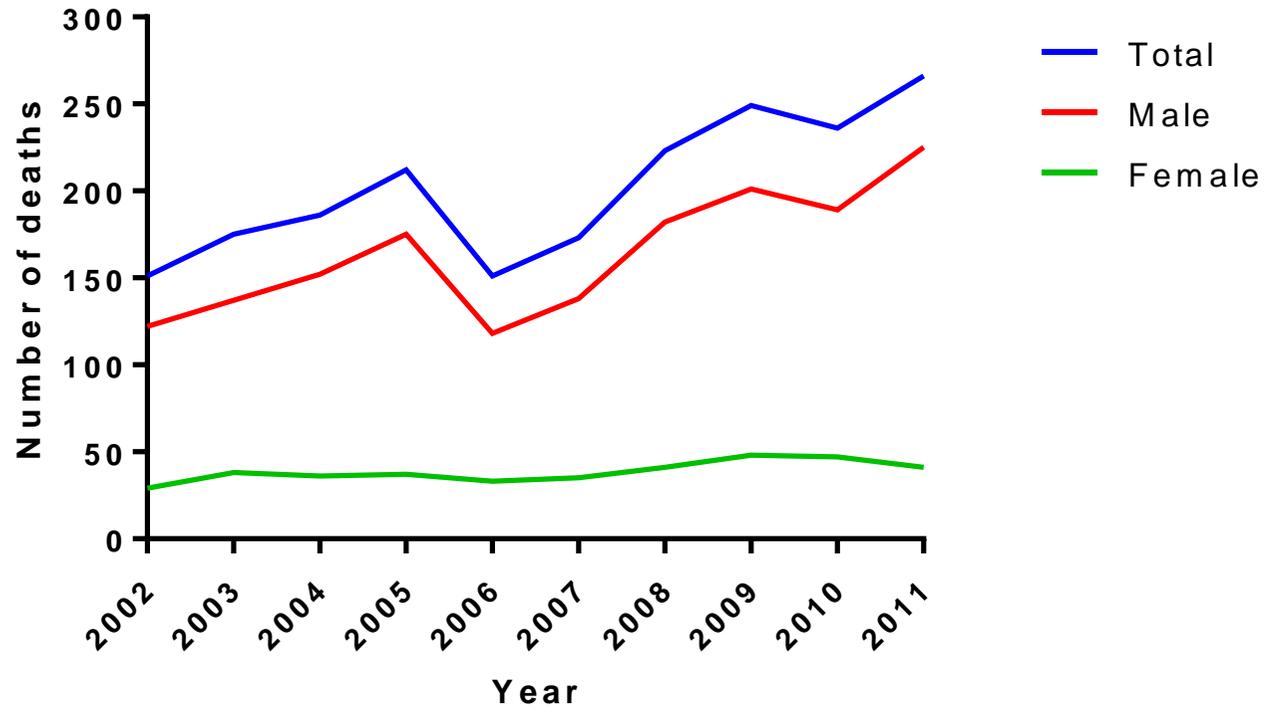
The number of accidental deaths due to pharmaceutical opioids and other illicit substances increased from 151 in 2002 to 266 in 2011 (Figure 3.3), representing a 1.7-fold increase. The rate of increase was higher for males (1.8-fold) than females (1.4-fold). The rate of accidental poisoning deaths increased over the time period from 0.78 to 1.19 deaths per 100 000 population.

## **3.4 Discussion**

This report confirms and extends previous findings documenting the escalation of prescription opioid use in Australia. This study found that opioid utilisation has continued to increase at a striking rate since our previous report just 5 years ago.<sup>11</sup> The use of buprenorphine and fentanyl combined has escalated since that report and their combined total cost to government now exceeds that for oxycodone. We found an increase in the past decade in the number of hospitalisations related to prescribed opioids and the number of accidental deaths due to illicit drugs and pharmaceutical opioids. These data indicate the need for broad new strategies to manage opioid use.

A number of explanations may account for the exponential increase in opioid utilisation in Australia in the past 20 years including changes in PBS listings, prescriber/patient preference for specific opioids, the ageing population, increase in prevalence of pain and/or reduced availability of illicit drugs.

Figure 3.3 Number of accidental deaths due to illicit drugs and pharmaceutical opioids in Australia: 2002 – 2011



The increase in opioid dispensing may reflect PBS-listing changes. The increase in oxycodone and tramadol dispensing from 2000 (Figure 3.1A) is likely due to the extension of the PBS-listings for opioid analgesics to treat both cancer and non-cancer pain.<sup>24</sup> Moreover, in 2004 the maximum quantity and number of repeat PBS prescriptions allowed to be prescribed per physician visit increased for strong opioids including oxycodone, hydromorphone, methadone and morphine. Tramadol is a weaker analgesic compared with these opioids and it appears that when doctors were given the opportunity to prescribe larger quantities of stronger opioids, the rate of tramadol dispensing decreased. Despite the broadening of restrictions for all opioids, oxycodone has experienced the greatest increase in dispensing. These data suggest the increase in pack size of oxycodone influenced prescribing practices.

A recent Australian study found a significant proportion of older persons initiating oxycodone for non-cancer pain had not been treated in the previous 12 months with any other analgesic.<sup>25</sup> This is a concern as PBS-listed opioids are funded as 'second line treatment for pain not relieved by non-narcotic analgesics' such as paracetamol. This may be due to Australian prescribers being less aware of the best practice prescribing guidelines for analgesia. An alternate explanation may be due to prescriber preference. In Denmark, hospital physicians and general practitioners preferred to prescribe oxycodone over morphine to opioid naïve patients,<sup>26</sup> and in Spain, oxycodone and fentanyl may be prescribed instead of morphine, due to the latter drugs association with the end of life.<sup>27</sup>

Australia's ageing population may also account for the observed increase in opioid utilisation. Of all oxycodone and fentanyl dispensed, the rate of utilisation in the  $\geq 80$

year age group is higher than any other age group.<sup>14,15</sup> Rates of concomitant prescription drug use are also high in the elderly,<sup>28</sup> as well as an increased sensitivity to drug toxicity suggests opioid-related harm may be a particular issue in this age group.

The prevalence of pain has increased at a population level in Australia since 1995, consequently we would expect an increase in the demand for analgesia. According to Australia's National Health Survey, the reported prevalence of body pain was 57% in 1995 and increased to 68% in 2008 as assessed by the SF-36, a validated quality of life measure. Similarly, there was an increase in self-reported severe/very severe pain, from 7% in 1995 to 10% in 2008.<sup>29</sup> Despite the increase in opioid use and availability of different opioids and formulations, there remain many cases where pain is undertreated.<sup>30</sup>

The limited availability of illicit drugs may also impact on prescribed opioid utilisation. Australia experienced a heroin drought in 2001, and due to the reduction of heroin availability, some drug seekers may have sought pharmaceutical opioids as a replacement.<sup>13,31</sup>

#### *3.4.1 Cost of opioid utilisation*

Since 1992, the Australian government paid over \$2 billion in prescription opioid subsidies. The cost of opioids has risen significantly in the past 5 years, primarily due to the increase in dispensing of buprenorphine and fentanyl. The newer opioids are more expensive as they include controlled release preparations. This increased rate of prescribing most likely accounts for the extraordinary 32-fold increase in cost to the government compared with the 15-fold increase in opioid dispensing episodes. This is likely to be of concern for the

Australian government, as the utilisation and hence cost to the government for these opioids is yet to plateau (Figures 3.1A and 3.1B).

Of note is the escalating cost of buprenorphine and fentanyl. Since 2005, the PBS has subsidised buprenorphine transdermal patches to treat pain costing between \$24.67 and \$56.18 per dispensing. The buprenorphine patch singularly accounts for all buprenorphine use and has been the driver for increased buprenorphine use in other jurisdictions.<sup>27,32</sup> For fentanyl, the transdermal patch and lozenge are PBS-subsidised. From 2006 to 2008 the fentanyl patch was the only PBS-listed fentanyl formulation costing between \$41.53 and \$171.63 per dispensing. The lozenge was introduced in 2008 costing between \$114.62 and \$680.23 per dispensing and used exclusively in palliative care. We note the significant upward trend in number of dispensings and cost did not appear to be impacted by the introduction of the lozenge, meaning that the patch is likely the biggest contributor to volume and cost. Other jurisdictions have also reported the transdermal patch to be the primary driver of increased fentanyl use.<sup>27,32,33</sup>

### *3.4.2 Opioid-related harms*

There is a plethora of literature reporting the medical harms associated with opioid use<sup>14,15,34-44</sup> and all of these findings indicate opioid-related harms are increasing.

Based on publically available data we were able to examine opioid-related hospitalisations and accidental poisoning deaths, both of which have been increasing since the early 2000s. These patterns are consistent with the US with one notable exception. In Australia, between 2002 and 2011 the rate of increase in opioid-related deaths was higher in males (1.8-fold)

than females (1.4-fold). In contrast, in the US, between 1999 and 2010, the rate of increase for opioid-related deaths was higher for females (400%) compared to males (265%).<sup>45</sup> However, the absolute number of overdose deaths in males exceeded the number in females in both countries. One explanation for this discrepancy may be the inclusion of illicit drugs in the Australian cause of death data, as males are more likely to overdose on illicit substances than females.

The strengths of this report include combining multiple national data sources to document opioid prescription availability, utilisation, costs and related harms in the Australian context. To our knowledge, no previous Australian study has synthesised the information presented from these data sources to describe the rise and consequences of an increase in the use of all PBS-funded opioids. This overview also demonstrates the wide array of high quality data freely available documenting trends of opioid use, costs and harms that can be utilised to assess the effectiveness of strategies to contain usage.

This paper relies on routinely collected datasets, which are not without limitations as described above. One of the main limitations of the PBS dataset is it underestimates whole-of-population use, making the accuracy of the trends uncertain and all interpretations are subject to this limitation. However, a recent study analysing data from the state of Queensland found that PBS data correlate closely with data derived from State-based mandatory reporting for all Schedule 8 (drugs with a high abuse potential) opioid prescriptions.<sup>17</sup> All opioids reported in this study are Schedule 8, except tramadol, listed as a Schedule 4 drug indicating a reduced risk of abuse.

The present study shows that opioid use is increasing in Australia, with no sign of stabilisation. Within the same time period, the number of opioid-related hospitalisations and deaths has also increased. A national pharmaceutical drug strategy has been devised<sup>46</sup> but does not appear to have impacted on the rising opioid use to date. We recommend further population based studies exploring individual level data on opioid use. Such studies could assess the safety of opioids through identifying risky prescribing patterns, ensure prescribing patterns are consistent with health policy guidelines and limit concomitant use of opioids with other potentially dangerous drugs such as benzodiazepines, particularly in the elderly. We also need to understand patterns of prescription drug use that may indicate evolving dependence on opioids. This information could in turn be communicated to prescribers to guide interventions aimed at preventing opioid dependence and consequent harms.

### ***3.5 Conclusions***

Opioid analgesics are effective in treating both cancer and non-cancer pain. However, the ongoing increase in opioid utilisation and related harms in Australia demonstrates there is an urgent need for further research to understand patterns of opioid use that moves from aggregated data to individual level analyses for the Australian population. Through this research we hope to generate strategies to optimise the use of opioid analgesics and pain relief with minimal complications.

### 3.6 References

1. Ballantyne JC. Chronic opioid therapy and its utility in different populations. *Pain*. 2012; 153(12): 2303-2304.
2. Kissin I. Long-term opioid treatment of chronic nonmalignant pain: unproven efficacy and neglected safety? *J Pain Res*. 2013; 6: 513.
3. Kuehn BM. Opioid prescriptions soar: increase in legitimate use as well as abuse. *JAMA*. 2007; 297(3): 249-251.
4. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician*. 2010; 13(5): 401-435.
5. Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, et al. Opioid epidemic in the United States. *Pain Physician*. 2012; 15(3 Suppl): ES9-38.
6. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008; 11(2 Suppl): S63-88.
7. Casati A, Sedefov R, Pfeiffer-Gerschel T. Misuse of medicines in the European Union: a systematic review of the literature. *Eur Addict Res*. 2012; 18(5): 228-245.
8. The Royal Australian & New Zealand College of Psychiatrists. Response to the National Pharmaceutical Drug Misuse Strategy. 2011; <https://www.ranzcp.org/Files/ranzcp-attachments/.../sub61-pdf.aspx>. Accessed 1 December 2013.
9. Nicholas R, Lee N, Roche A. Pharmaceutical drug misuse in Australia: complex problems, balanced responses. In: National Centre for Education and Training on Addiction (NCETA), ed. Adelaide: Flinders University; 2011.

10. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, et al. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend.* 2003; 69(3): 215-232.
11. Leong M, Murnion B, Haber PS. Examination of opioid prescribing in Australia from 1992 to 2007. *Intern Med J.* 2009; 39(10): 676-681.
12. Berbatis CG, Sunderland VB, Bulsara M, Lintzeris N. Trends in licit opioid use in Australia, 1984-1998: comparative analysis of international and jurisdictional data. *Med J Aust.* 2000; 173(10): 524-527.
13. Degenhardt L, Black E, Breen C, Bruno R, Kinner S. Trends in morphine prescriptions, illicit morphine use and associated harms among regular injecting drug users in Australia. *Drug Alcohol Rev.* 2006; 25(5): 403-412.
14. Roxburgh A, Burns L, Drummer OH, Pilgrim J, Farrell M, et al. Trends in fentanyl prescriptions and fentanyl-related mortality in Australia. *Drug Alcohol Rev.* 2013; 32(3): 269-275.
15. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. *Med J Aust.* 2011; 195(5): 280-284.
16. Bell JR. Australian trends in opioid prescribing for chronic non-cancer pain, 1986-1996. *Med J Aust.* 1997; 167(1): 26-29.
17. Hollingworth SA, Symons M, Khatun M, Loveday B, Ballantyne S, et al. Prescribing databases can be used to monitor trends in opioid analgesic prescribing in Australia. *Aust N Z J Public Health.* 2013; 37(2): 132-138.
18. Rintoul AC, Dobbin MDH, Drummer OH, Ozanne-Smith J. Increasing deaths involving oxycodone, Victoria, Australia, 2000-09. *Inj Prev.* 2011; 17(4): 254-259.

19. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders - Diagnostic Criteria for Research*. Geneva: WHO; 1993.
20. Australian Institute of Health and Welfare. Separation statistics by principal diagnosis in ICD-10-AM, 1998-99 to 2007-08. 2013; <http://www.aihw.gov.au/data-cube/?id=10737418525>. Accessed 1 October 2013.
21. Australian Institute of Health and Welfare. Separation statistics by principal diagnosis in ICD-10-AM, 2008-09 to 2009-10. 2013; <http://www.aihw.gov.au/hospitals-data-cube/?id=10737419429>. Accessed 1 October 2013.
22. Henderson T, Shephard J, Sundararajan V. Quality of diagnosis and procedure coding in ICD-10 administrative data. *Med Care*. 2006; 44(11): 1011-1019.
23. Australian Bureau of Statistics. 3303.0 Causes of Death, Australia, 2011. 2013; <http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3303.02011?OpenDocument>. Accessed 4 October 2013.
24. Australian Government Department of Health. PBAC Outcomes. <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes>. Accessed 10 October 2013.
25. Gadzhanova S, Bell JS, Roughead EE. What analgesics do older people use prior to initiating oxycodone for non-cancer pain? A retrospective database study. *Drugs Aging*. 2013; 30(11): 921-926.
26. Poulsen KK, Andersen SE, Moreno SI, Glintborg D, Thirstrup S, et al. General practitioners' and hospital physicians' preference for morphine or oxycodone as first-time choice for a strong opioid: a national register-based study. *Basic Clin Pharmacol Toxicol*. 2013; 112(2): 110-115.

27. Garcia del Pozo J, Carvajal A, Vilorio JM, Velasco A, Garcia del Pozo V. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *Eur J Clin Pharmacol*. 2008; 64(4): 411-415.
28. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014; 13(1): 57-65.
29. Australian Bureau of Statistics. Characteristics of bodily pain in Australia. 2012; <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4841.0Chapter12011>. Accessed 14 November 2013.
30. Fairchild A. Under-treatment of cancer pain. *Curr Opin Support Palliat Care*. 2010; 4(1): 11-15.
31. Longo MC, Henry-Edwards SM, Humeniuk RE, Christie P, Ali RL. Impact of the heroin 'drought' on patterns of drug use and drug-related harms. *Drug Alcohol Rev*. 2004; 23(2): 143-150.
32. Fredheim OM, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007 – pharmacoepidemiological data from a complete national prescription database in Norway. *Eur J Pain (London, England)*. 2010; 14(3): 289-294.
33. Hudec R, Tisonova J, Bozekova L, Foltan V. Trends in consumption of opioid analgesics in Slovak Republic during 1998-2002. *Eur J Clin Pharmacol*. 2004; 60(6): 445-448.
34. Schumann H, Erickson T, Thompson TM, Zautcke JL, Denton JS. Fentanyl epidemic in Chicago, Illinois and surrounding Cook County. *Clin Toxicol*. 2008; 46(6): 501-506.
35. Porucznik CA, Johnson EM, Sauer B, Crook J, Rolfs RT. Studying adverse events related to prescription opioids: the Utah experience. *Pain Med*. 2011; 12(Suppl 2): S16-25.

36. Stannard C. Opioids in the UK: what's the problem? *BMJ*. 2013; 347: f5108.
37. Unick GJ, Rosenblum D, Mars S, Ciccarone D. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993-2009. *PLoS ONE*. 2013; 8(2): e54496.
38. Coben JH, Davis SM, Furbee PM, Sikora RD, Tillotson RD, et al. Hospitalizations for poisoning by prescription opioids, sedatives, and tranquilizers.[Erratum appears in *Am J Prev Med*. 2010 Dec;39(6):613]. *Am J Prev Med*. 2010; 38(5): 517-524.
39. Lloyd BK, McElwee PR. Trends over time in characteristics of pharmaceutical drug-related ambulance attendances in Melbourne. *Drug Alcohol Rev*. 2011; 30(3): 271-280.
40. Hall AJ, Logan JE, Toblin RL, Kaplin JA, Kraner JC, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008; 300(22): 2613-2620.
41. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA*. 2013; 309(7): 657-659.
42. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, et al. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med*. 2012; 13(1): 87-95.
43. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, et al. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction*. 2009; 104(9): 1541-1548.
44. Darnall BD, Stacey BR, Chou R. Medical and psychological risks and consequences of long-term opioid therapy in women. *Pain Med*. 2012; 13(9): 1181-1211.
45. Centers for Disease Control and Prevention. Vital signs: Prescription painkiller overdoses: a growing epidemic, especially among women. 2013;

<http://www.cdc.gov/vitalsigns/PrescriptionPainkillerOverdoses/index.html>.

Accessed 1 October 2013.

46. The National Centre for Education and Training on Addiction. National Pharmaceutical Drug Misuse Strategy.

[http://nceta.flinders.edu.au/society/projects\\_and\\_research/national-pharmaceutical-drug-misuse-strategy/](http://nceta.flinders.edu.au/society/projects_and_research/national-pharmaceutical-drug-misuse-strategy/). Accessed 1 December 2013.

***Chapter Four: Benchmarking prescription drug access patterns in dispensing claims: a method for identifying high and potentially harmful opioid use in Australia and Canada?***

Our systematic review in Chapter Two highlighted the major methodological limitations in quantifying prescription drug misuse based on pharmaceutical claims. The dominant approach is to dichotomise use and misuse based on a specific measure with generally limited empirical evidence justifying these choices. Few studies reported the spectrum of prescription drug access. Reporting the spectrum of use or access across jurisdictions and drug classes will allow us to: understand the norms of drug access and assess what factors may impact on access including abuse potential, policies, healthcare setting/arrangement and patient factors. Over the next three chapters, we present two methodologies to examine prescription opioid use and access using alternative methods to those predominantly used in the global literature.

In this chapter, we examine the spectrum of opioid access, based on number of unique prescribers, and compare against statins, a drug class with no known abuse potential. This approach will allow us to compare access patterns and identify differences based on abuse potential of the drug class. This method was replicated in British Columbia, Canada, to determine whether prescriber access patterns for both drug classes are similar across jurisdictions with universal healthcare arrangements.

This chapter is currently under consideration for publication; it has been peer-reviewed twice by the *Journal of Pharmaceutical Health Services Research*; we responded to reviewers' comments on 7 November 2016.

Bianca Blanch, Emilie Gladstone, Kate Smolina, Nicholas A. Buckley, Emily A. Karanges, Steven G. Morgan, Sallie-Anne Pearson. Benchmarking prescription drug access patterns in dispensing claims: a method for identifying high and potentially harmful opioid use in Australia and Canada?

Formatting note: To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. The key points and abstract are formatted according to the *Journal of Pharmaceutical Health Services Research* style guide. We provide the reference list at the end of each chapter. Supplementary materials are located after the references for this chapter.

## ***Key Points***

- We used number of unique prescribers to measure access patterns for opioids and statins and found the vast majority of persons visited one or two prescribers to access both prescription drug classes in 2011, which was consistent across jurisdictions.
- Accessing  $\geq 4$  prescribers represents unusual drug access patterns for both prescription drug classes; however, the number of persons accessing  $\geq 7$  prescribers was at least 35-fold higher in opioids compared to statins in both Australia and British Columbia.
- Our benchmarking approach has the potential to inform post-market surveillance activities and flag outlying access patterns; however, further research is required to validate this measure.

## ***Abstract***

### *Objective*

We use dispensing claims to benchmark prescriber access patterns for opioids against statins (a drug class with no known abuse potential) in Australia and British Columbia, Canada.

### *Study design*

Observational cohort study.

### *Methods*

We used pharmaceutical claims from the Australian Pharmaceutical Benefits Scheme and British Columbian PharmaCare. Specifically, we used individual-level claims in adults with complete capture of subsidised prescription drugs and  $\geq 1$  opioid or statin dispensing(s) in 2011. We report the distribution of unique opioid and statin prescribers overall, by age and jurisdiction.

### *Results*

In 2011, the vast majority of persons visited one or two prescribers to access opioids and statins (Australia: 86.0% vs. 91.5%; British Columbia: 90.2% vs. 92.1%, respectively). The proportion of persons accessing  $\geq 4$  prescribers was higher for persons dispensed opioids compared to statins (Australia: 6.5% vs. 1.3%; British Columbia: 4.2% vs. 1.7%, respectively). For opioids, a greater proportion of persons aged  $< 65$  years accessed  $\geq 4$  opioid prescribers compared to their older counterparts ( $\geq 65$  years); these differences were more pronounced in British Columbians receiving income assistance.

### *Conclusions*

Benchmarking the entire spectrum of use for specific prescription drug classes could provide a useful tool for informing post-market surveillance activities and may identify potentially problematic drug access behaviour(s).

## **4.1 Introduction**

Prescription opioid use and related harms have increased globally.<sup>1</sup> In the period 2002-2011, prescription opioid use at least doubled in Australia, Canada and US,<sup>2,3</sup> accompanied by considerable increases in opioid-related hospitalisations and deaths.<sup>4-7</sup> Not surprisingly, the increase in opioid consumption and associated harms have raised concerns regarding prescription opioid misuse, abuse and addiction and identified the need for a public health response to promote the safe and appropriate use of opioids. The first necessary step to evidence-informed action is to quantify the extent of the problem. Consequently, in 2014 the US Food and Drug Administration endorsed the use of population-based routinely collected health data, including pharmaceutical claims, to quantify opioid misuse.<sup>8</sup>

We recently published a systematic review synthesising 13 years of international literature to identify common methods for examining prescription drug misuse in pharmaceutical claims.<sup>9</sup> Across the 52 reviewed studies, opioids were the most frequently studied drug class and accessing multiple prescribers (or ‘doctor shopping’) was the most commonly used metric to define misuse.<sup>9,10</sup> Access patterns were frequently dichotomised with a threshold applied to delineate use from misuse. These thresholds varied between studies and were generally informed by existing literature or expert opinion. Importantly, few studies explored the full spectrum of access patterns, reported the norms of access or compared prescriber access patterns across drug classes with varying abuse potential. Our review also highlighted that younger persons were more likely to ‘doctor shop’ or visit a larger number of prescribers to access opioids compared with their older counterparts.<sup>11-14</sup>

Therefore, our objective is to use pharmaceutical claims to benchmark (or compare) opioid prescriber access patterns against a drug class with no known abuse potential. Specifically, we will contrast opioid and statin access patterns, overall and by age. We will apply this methodology in Australia and British Columbia, Canada to demonstrate the utility of benchmarking prescription drug access patterns across different healthcare settings.

## **4.2 Methods**

### *4.2.1 Study design*

This was an observational study of persons with  $\geq 1$  opioid or statin dispensing(s) across two healthcare settings. The study analysed data from the calendar year of 2011, the latest common year of data across jurisdictions.

### *4.2.2 Settings*

Australia and Canada have universal healthcare arrangements including subsidised access to prescription drugs via Australia's Pharmaceutical Benefits Scheme (PBS)<sup>15</sup> and PharmaCare in British Columbia.<sup>16</sup> In 2011, the population of Australia and British Columbia were 21.5 and 4.4 million respectively.

### *4.2.3 Data sources*

#### *4.2.3.1 Australia*

The Australian Government Department of Human Services (DHS) provided a de-identified, standardised dataset of drug dispensing claims from a random 10% sample of PBS beneficiaries.<sup>15</sup> To ensure complete ascertainment of dispensings, we restricted our Australian analyses to individuals with concessional beneficiary status (low income,

unemployment, sick, disability, single parent or aged pensioners) for the entirety of 2011. Concessional beneficiaries have a lower copayment threshold (AU\$5.60 in 2011) than general beneficiaries (AU\$34.20 in 2011); consequently, all PBS-dispensed drugs for the former attract government reimbursement. Concessional beneficiaries represent 25% of the PBS-eligible Australian population.<sup>17</sup> Dispensing records included: patient unique identifier, sex, month/year of birth, Anatomical Therapeutic Chemical (ATC) classification code,<sup>18</sup> date of supply, formulation, strength, quantity dispensed, beneficiary status and prescriber unique identifier.

#### 4.2.3.2 British Columbia

Population Data British Columbia provided de-identified data for all British Columbians, with the exception of beneficiaries of federal health programs (4% of the population whose dispensing records were not recorded in our dataset). Pharmaceutical data for British Columbians were from PharmaNet, a province-wide system capturing all drugs dispensed at retail pharmacies. Residents of British Columbia were covered by a universal, income-based drug plan (Fair PharmaCare) that involved deductibles set as a percentage of household income. A minority of these British Columbian residents received income assistance (PharmaCare Plan C) and did not pay any copayments under the PharmaCare program. Persons eligible for income assistance comprised 4% of the total British Columbian population in 2011. Dispensing records included all variables available in our Australian data (excluding beneficiary status) as well as days of therapy, cost and type of coverage.

#### *4.2.4 Prescription drugs of interest*

We included all publically subsidised opioid analgesics and statins with ATC codes N02A and C10AA respectively. Opioid analgesics were listed on both schemes to treat episodic, chronic, cancer or non-cancer pain, in contrast, statins lower blood cholesterol levels and were prescribed for both primary and secondary prevention of cardiovascular disease. Statins were chosen as the comparator drug class as they are commonly dispensed in both jurisdictions and have no known abuse potential. Supplementary Table 4.1 details the prescription drugs common and unique to each jurisdiction.

#### *4.2.5 Cohort inclusion criteria*

We derived two cohorts based on dispensing history for prescription drugs of interest in each jurisdiction; persons could be part of both the opioid and statin cohorts. The cohorts in both jurisdictions included persons aged  $\geq 18$  years (as of January 1, 2011),  $\geq 1$  opioid or statin dispensing(s) in 2011 and alive for the entire year (Supplementary Figure 4.1A).

To ensure complete capture of subsidised prescription drugs for all individuals in each jurisdiction, the Australian cohort was restricted to persons with a concessional beneficiary status for the entire year and the British Columbian cohort was restricted to residents living in the province for all of 2011. We also stratified the British Columbian cohort by receipt of income assistance<sup>19</sup> defined as  $\geq 1$  opioid or statin dispensing(s) in 2011 reimbursed by PharmaCare Plan C. Of note, these individuals may not have received income assistance for the entirety of 2011. Persons receiving income assistance comprised 10.5% of the opioid cohort and 5.4% of the statin cohort in British Columbia (Supplementary Figure 4.1B).

To ensure complete capture of subsidised prescription drugs for all individuals in each jurisdiction, the Australian cohort was restricted to persons with a concessional beneficiary status for the entire year and the British Columbian cohort was restricted to residents living in the province for all of 2011. We also stratified the British Columbian cohort by receipt of income assistance<sup>19</sup> defined as  $\geq 1$  opioid or statin dispensing(s) in 2011 reimbursed by PharmaCare Plan C. Of note, these individuals may not have received income assistance for the entirety of 2011. Persons receiving income assistance comprised 10.5% of the opioid cohort and 5.4% of the statin cohort in British Columbia (Supplementary Figure 4.1B).

#### *4.2.7 Statistical analysis*

Our primary outcome measure was number of unique prescribers of dispensed opioids or statins in 2011. In both jurisdictions, we report the distribution of number of prescribers visited to access these drugs overall and by age group (18-44; 45-64;  $\geq 65$  years), and in British Columbia, by persons receiving income assistance. The Australian analyses were completed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and the British Columbian analyses were completed using Stata 13.1 (College Station, TX: StataCorp LP).

### **4.3 Results**

#### *4.3.1 Cohort demographics*

The opioid cohorts in both jurisdictions were predominantly female (Australia: 59.6%; British Columbia [all]: 53.0%). The Australian and British Columbian cohorts had median ages of 64 (interquartile range [IQR]: 45-75) and 51 (IQR: 38-64) years respectively (Table 4.1). In Australia in 2011, codeine (27.8%) and oxycodone (25.6%) together comprised more than half of all opioid dispensings. In British Columbia, codeine alone accounted for almost

half (46.7%) of all opioid dispensings, while oxycodone dispensings were comparatively low (11.7%) (Table 4.2).

The Australian statin cohort was predominantly female (55.2%) while the British Columbian statin cohort was mostly male (43.2% female). The median ages were 71 (IQR: 65-78) and 66 (IQR: 58-75) years respectively.

Approximately, 10.5% of British Columbians dispensed an opioid in 2011 received income assistance (Supplementary Figure 4.1B), yet they obtained approximately one-quarter (27.6%; n = 594 689) of all opioid dispensings (Table 4.2). Furthermore, 5.4% of British Columbians dispensed a statin in 2011 received income assistance (Supplementary Figure 4.1B) and obtained 10.7% (n = 264 088) of all statin dispensings (Table 4.2).

**Table 4.1** Cohort demographics

	Australia	British Columbia	
		All	Income Assistance
<b>Opioid users (N)</b>	<b>118 125</b>	<b>482 591</b>	<b>50 633</b>
Age (median, IQR)	64 (45-75)	51 (38-64)	48 (37-56)
Age groups (N, %)			
<i>18-44 years</i>	28 752 (24.3)	173 875 (36.0)	20 473 (40.4)
<i>45-64 years</i>	31 424 (26.6)	195 585 (40.5)	25 613 (50.6)
<i>≥65 years</i>	57 949 (49.1)	113 131 (23.4)	4 547 (9.0)
Female sex (N, %)	70 369 (59.6)	255 174 (53.0)	25 038 (49.4)
<b>Statin users (N)</b>	<b>147 728</b>	<b>397 345</b>	<b>21 267</b>
Age (median, IQR)	71 (65-78)	66 (58-75)	59 (52-67)
Age groups (N, %)			
<i>18-44 years</i>	3 672 (2.5)	15 715 (4.0)	2 045 (9.6)
<i>45-64 years</i>	30 812 (20.9)	169 191 (42.6)	12 866 (60.5)
<i>≥65 years</i>	113 244 (76.7)	212 439 (53.5)	6 356 (29.9)
Female sex (N, %)	81 542 (55.2)	171 554 (43.2)	10 162 (47.8)

**Table 4.2** Three most frequently dispensed prescription drugs by class and jurisdiction (2011)

	Australia (%)	British Columbia	
		All (%)	Income Assistance (%)
<b>Opioid dispensings (N)</b>	<b>737 016</b>	<b>2 155 678</b>	<b>594 689</b>
	Codeine (27.8)	Codeine (46.7)	Codeine (42.5)
	Oxycodone (25.6)	Morphine (14.2)	Morphine (27.1)
	Tramadol (20.4)	Hydromorphone (14.2)	Hydromorphone (14.6)
<b>Statins dispensings (N)</b>	<b>1 444 407</b>	<b>2 417 617</b>	<b>264 088</b>
	Atorvastatin (47.3)	Atorvastatin (45.8)	Atorvastatin (48.6)
	Rosuvastatin (24.8)	Rosuvastatin (31.0)	Rosuvastatin (27.6)
	Simvastatin (22.0)	Simvastatin (19.1)	Simvastatin (20.2)

### 4.3.2 Number of unique prescribers

#### 4.3.2.1 Overall prescriber access patterns

In Australia and British Columbia (all), most people accessed one or two prescribers for opioids (86.0% in Australia and 90.2% in British Columbia) and statins (91.5% in Australia and 92.1% in British Columbia) (Figures 4.1A-C; Table 4.3). The majority of the British Columbian income assistance group also accessed one or two prescribers, but the proportion of persons with this access pattern were lower for both opioids (74.0%) and statins (85.0%) compared to the entire British Columbian cohort. In both jurisdictions, the proportion of persons accessing  $\geq 4$  prescribers was higher for opioids than statins (Australia: 6.5% and 1.3%; British Columbia [all]: 4.2% and 1.7%; [income assistance]: 14.3% and 4.9% respectively). Further, a greater proportion of persons visited  $\geq 7$  prescribers to access opioids (Australia: 1.1%; British Columbia [all]: 0.7%; [income assistance]: 3.4%) than statins ( $\leq 0.3%$  in Australia, British Columbia [all] and [income assistance]). The 99<sup>th</sup> centile of the number of unique prescribers was higher for opioids than statins in both Australia (opioids: 7; statins: 4) and British Columbia ([all]: opioids: 6; statins: 4), particularly for British Columbians receiving income assistance (opioids: 10; statins: 5).

**Figure 4.1** Violin plot distribution of unique number of prescribers by drug class and

jurisdiction

Figure 4.1A Australia

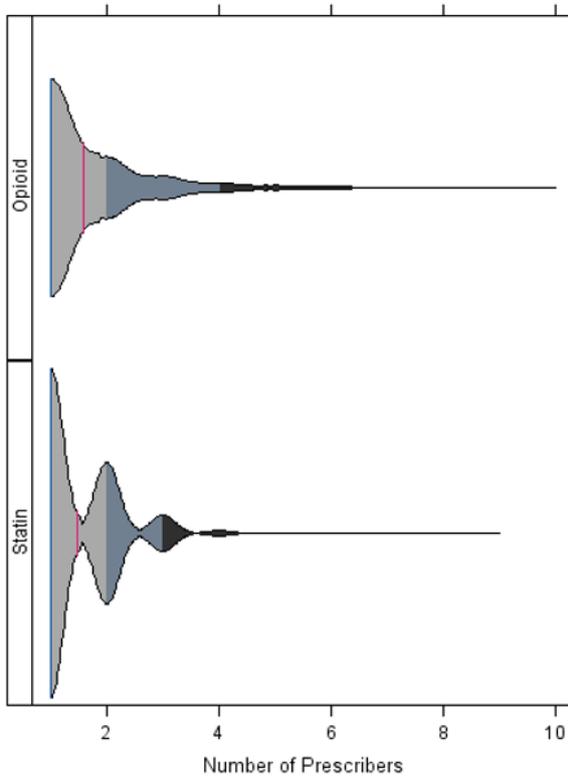


Figure 4.1B British Columbia: all

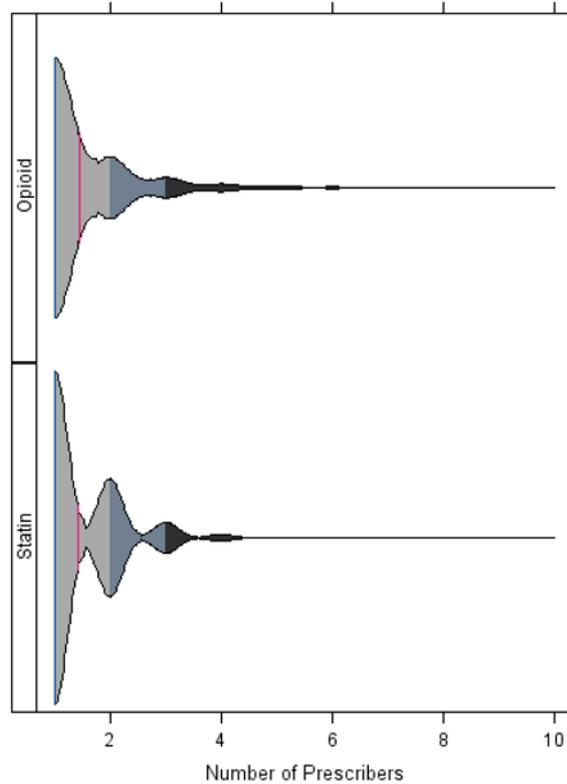
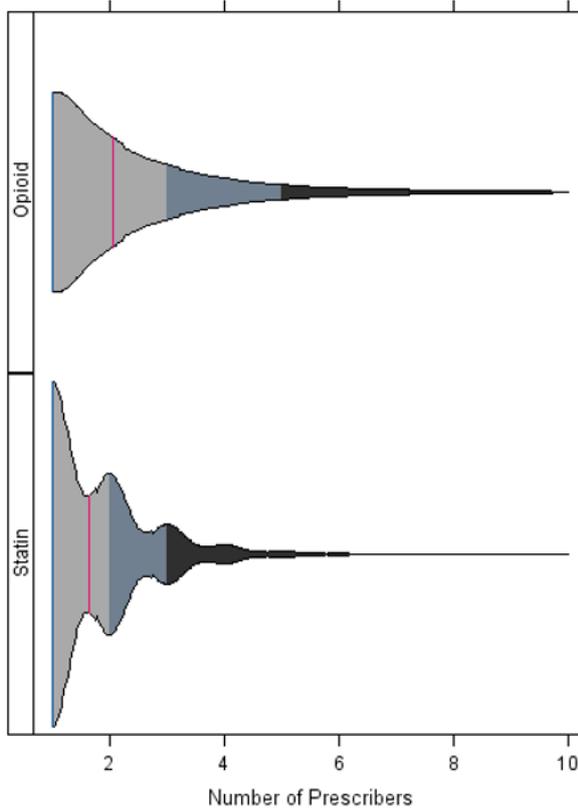


Figure 4.1C British Columbia: income assistance



Legend: 1<sup>st</sup> to 84<sup>th</sup> centiles in grey (median = 1 prescriber for all groups); 85<sup>th</sup> to 94<sup>th</sup> centiles in dark grey; ≥95<sup>th</sup> centiles in black. Mean = red line.

**Table 4.3.** Comparison of unique number of prescribers by prescription drug class and age group in Australia and British Columbia (2011)

Number of unique prescribers (age group [years])	Australia		British Columbia			
	Opioid (%) N = 118 125	Statin (%) N = 147 728	All		Income Assistance	
			Opioid (%) N = 482 591	Statin (%) N = 397 345	Opioid (%) N = 50 633	Statin (%) N = 21 267
<b>1 prescriber</b>						
<b>All ages</b>	<b>66.1</b>	<b>63.9</b>	<b>72.8</b>	<b>68.0</b>	<b>50.8</b>	<b>57.8</b>
18-44	68.4	65.0	76.2	70.8	51.5	57.0
45-64	63.8	62.1	70.6	68.4	49.0	57.3
≥65	66.1	64.3	71.3	67.4	57.9	59.2
<b>2 prescribers</b>						
<b>All ages</b>	<b>19.9</b>	<b>27.6</b>	<b>17.4</b>	<b>24.1</b>	<b>23.2</b>	<b>27.2</b>
18-44	17.8	25.1	15.0	21.2	22.2	26.5
45-64	20.5	28.4	18.3	23.6	23.9	27.2
≥65	20.7	27.5	19.5	24.6	24.2	27.6
<b>3 prescribers</b>						
<b>All ages</b>	<b>7.5</b>	<b>7.2</b>	<b>5.6</b>	<b>6.2</b>	<b>11.6</b>	<b>10.1</b>
18-44	6.4	7.6	4.7	5.7	10.6	10.0
45-64	8.3	7.9	6.3	6.2	12.7	10.4
≥65	7.6	7.0	6.0	6.3	10.1	9.3
<b>4-6 prescribers</b>						
<b>All ages</b>	<b>5.4</b>	<b>1.3</b>	<b>3.6</b>	<b>1.7</b>	<b>10.9</b>	<b>4.6</b>
18-44	5.5	2.2	3.3	2.2	11.3	5.8
45-64	5.9	1.6	4.1	1.7	11.3	4.9
≥65	5.0	1.2	3.0	1.6	6.8	3.8

**7-9 prescribers**

<b>All ages</b>	<b>0.7</b>	<b>0.0</b>	<b>0.5</b>	<b>0.0</b>	<b>2.3</b>	<b>0.2</b>
18-44	1.2	0.1	0.6	0.1	2.7	0.6
45-64	1.0	0.0	0.6	0.0	2.2	0.2
≥65	0.5	0.0	0.2	0.0	0.8	0.1

**≥10 prescribers**

<b>All ages</b>	<b>0.4</b>	<b>0.0</b>	<b>0.2</b>	<b>0.0</b>	<b>1.1</b>	<b>0.0</b>
18-44	0.7	0.0	0.3	0.0	1.7	0.1
45-64	0.4	0.0	0.2	0.0	0.9	0.0
≥65	0.1	0.0	0.0	0.0	0.2	0.0

---

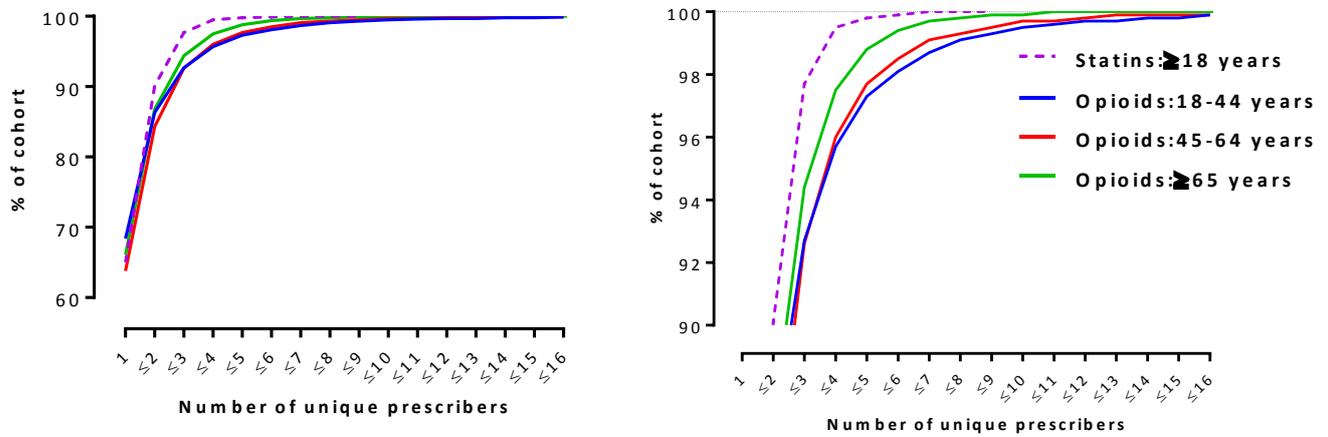
#### 4.3.2.2 Access patterns by age group

In Australia and British Columbia (all), opioid access patterns for persons aged 18-44 and 45-64 years were similar (Table 4.3). However, a greater proportion of persons aged <65 years accessed more opioid prescribers than their older counterparts ( $\geq 65$  years) (Figure 4.2). For example, a larger proportion of persons aged <65 years accessed  $\geq 7$  opioid prescribers compared to persons aged  $\geq 65$  years in Australia (18-44: 1.8%; 45-64: 1.4%;  $\geq 65$ : 0.6%) and British Columbia ([all]: 18-44: 0.9%; 45-64: 0.7%;  $\geq 65$ : 0.2%). There was no distinction in statin prescriber access patterns among age groups in Australia or British Columbia (all) (Supplementary Figure 4.2).

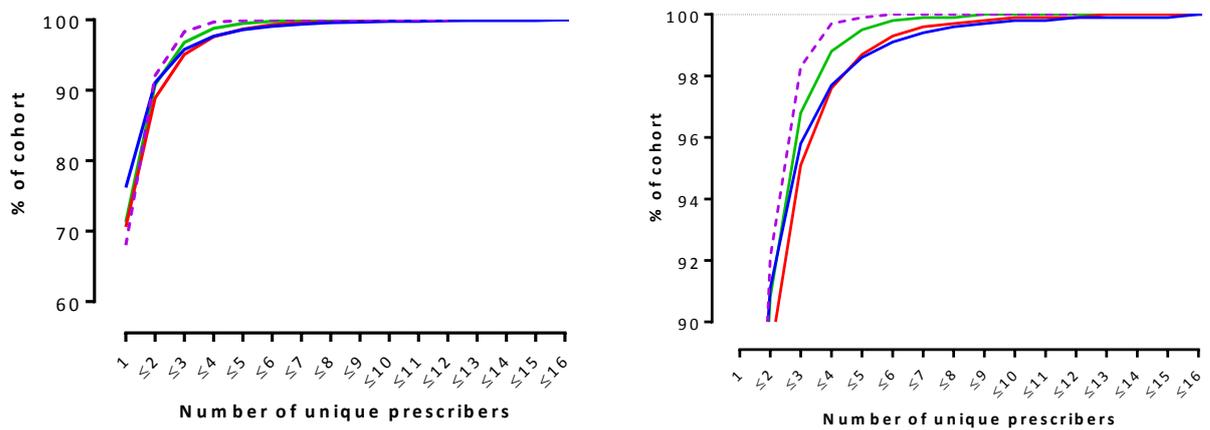
Among British Columbians receiving income assistance, a greater proportion of persons aged <65 years also accessed more opioid prescribers than their older counterparts ( $\geq 65$  years). However, within those aged <65 years, a larger proportion of persons aged 18-44 years accessed more opioid prescribers than those aged 45-64 years; apparent from  $\geq 5$  prescribers (18-44: 9.8%; 45-64: 8.3%) (Figure 4.2). Moreover, a greater proportion of persons aged 18-44 years, compared to those aged  $\geq 45$  years, accessed a larger number of statin prescribers, particularly from  $\geq 4$  prescribers (18-44: 6.6%; 45-64: 5.1%;  $\geq 65$ : 3.9%) (Supplementary Figure 4.2C).

**Figure 4.2** Cumulative frequency of unique statin or opioid prescribers by age group (2011)

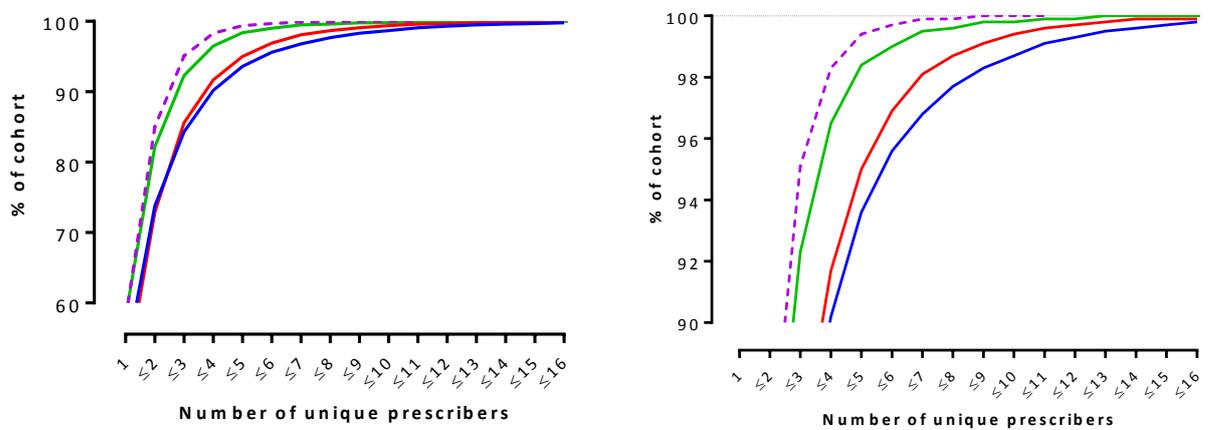
4.2A. Australian concessional beneficiaries: entire spectrum (left); upper decile (right)



4.2B. British Columbia (all): entire spectrum (left); upper decile (right)



4.2C. British Columbia (income assistance): entire spectrum (left); upper decile (right)



#### **4.4 Discussion**

Our benchmarking study demonstrated that the vast majority of persons accessed one or two prescribers for prescription opioids and statins in 2011. Two notable differences in the spectrum of prescriber access patterns were a greater proportion of persons accessing  $\geq 4$  prescribers for opioids compared to statins and persons aged  $< 65$  years accessed more opioid prescribers than their older counterparts ( $\geq 65$  years). These differences were more pronounced for British Columbians receiving income assistance. Interestingly, prescriber access patterns by drug class were remarkably similar across Australia and British Columbia despite their unique healthcare systems, prescription drugs listed on formularies and most frequently dispensed drugs. Together, these findings suggest benchmarking opioid access patterns against a drug class with no known abuse potential has utility in identifying potentially problematic access patterns across jurisdictions.

We demonstrated a greater proportion of persons accessing opioids are represented at the higher end of the access spectrum compared to statins; this was apparent at  $\geq 4$  prescribers but accentuated from  $\geq 7$  prescribers. The global literature investigating potential prescription drug misuse using pharmaceutical claims is dominated by studies based on thresholds that dichotomise access patterns, with higher access patterns signifying 'misuse.' This study highlights that using a 'doctor shopping' threshold of  $\geq 4$  prescribers in 12 months<sup>20</sup> may be indicative of problematic use, however, this threshold-based approach does not advance our understanding of the full spectrum of use nor how these access patterns compare with those of other drug classes. This benchmarking study provides a first step to developing alternative methods of examining extreme access behaviour which are potentially problematic and/or harmful.

Our findings suggest that when benchmarked against statin access patterns, a drug with no known abuse potential, a small proportion of persons from both jurisdictions engaged in opioid access behaviour that likely puts themselves or others at risk. In absolute terms this equates to around 13 500 Australians (numbers extrapolated from the 10% random sample) and 3 300 British Columbians visiting  $\geq 7$  unique opioid prescribers (Supplementary Table 4.2). In comparison,  $< 300$  Australians (number extrapolated from the 10% random sample) and  $< 100$  British Columbians accessed  $\geq 7$  unique statin prescribers in 2011.

Interestingly, we also identified a small but higher than expected proportion of persons visiting  $\geq 4$  statin prescribers. Statins are commonly prescribed in both jurisdictions as an original prescription with five refills; one prescription provides up to a 6-month supply. While it is not unreasonable to expect that a person may access up to three prescribers over a year due to variations in filling behaviour associated with altering the daily dose, switching/adding drugs etc., it is harder to understand how accessing  $\geq 4$  prescribers in a given year would reflect appropriate statin use. In absolute terms, this equates to approximately 3 200 Australians (extrapolated as above) and 6 700 British Columbians. This finding further highlights the benefits of examining the full spectrum of access patterns for all prescription drugs, not just those with known abuse potential.

There is considerable evidence demonstrating age differences in prescription opioid use and related harms across jurisdictions. For example, in Canada, younger persons have increased risk of opioid-related mortality.<sup>21</sup> Accordingly, we demonstrated notable differences in opioid prescriber access patterns by age, with a larger proportion of persons aged 18-44

years accessing more opioid prescribers than persons aged  $\geq 65$  years; reflecting findings from recent US studies.<sup>11-14, 22</sup> Interestingly, this pattern was particularly pronounced in British Columbians receiving income assistance for both opioids and statins.

It is difficult to ascertain what the behaviour at the higher end of the spectrum of use truly represents. Australian concessional beneficiaries account for only 25% of the PBS-eligible population<sup>17</sup> but the majority of PBS-subsidised prescription drug use.<sup>23</sup> In this study, we found British Columbians receiving income assistance also obtain large quantities of dispensings relative to their population size. These findings may simply reflect these populations are sicker than the general population.<sup>23</sup> However, persons exhibiting higher access patterns also obtain disproportionately large quantities of prescription drugs.<sup>24-27</sup> For example, in Australia in 2013, only 3.9% of persons accessed  $\geq 5$  opioid prescribers yet obtained 15.4% of all opioid dispensings.<sup>27</sup> So whether our findings reflect specific population characteristics, poor continuity of care, deliberate misuse, abuse or diversion (most likely observed at the highest end of the spectrum), it is almost certain the individual and societal consequences will be negative. Diversion for the purposes of selling or sharing prescription drugs with others has been reported in the literature;<sup>28-30</sup> this behaviour may be more common in persons who obtain drugs at minimum cost (such as through government subsidised healthcare programs) and given to individuals with higher copayments and/or restricted drug access. Accordingly, diversion may partly explain the greater proportion of persons on income assistance in British Columbia, who have no copayments, accessing higher numbers of statin and opioid prescribers.

Our study is not without limitations. This study used only one metric as a means of demonstrating the utility of benchmarking access patterns across drug classes. Our data did not allow us to determine if prescribers were from the same medical practice; feasibly persons could visit one practice but access multiple prescribers to access their prescription drugs. We chose statins as our comparator drug class because they have no known abuse potential, they are subsidised and widely used in both jurisdictions; used by persons of all ages; and are prescription only (not available over-the-counter). However, there are notable differences between opioid and statins; they have different medical indications; statins are most likely to be used chronically, unlike opioids that can be used either episodically or chronically, and different restrictions on access. Generally, in both jurisdictions, a maximum of a 30-day opioid supply is provided per prescription compared to a 6-month supply for statins. Consequently, persons with multiple opioid dispensings are required to visit prescribers more frequently compared to statins. For these reasons, more research is warranted to further explore this methodology by benchmarking other drug classes with different parameters for comparison.

The generalisability of our findings are uncertain, but it is encouraging that we demonstrated many similarities in access patterns by drug class across two jurisdictions. Further research in other healthcare settings should form part of the ongoing research agenda. The Australian cohort was restricted to persons with complete ascertainment of their prescription drugs (concessional beneficiaries). From April 2012, DHS captured all PBS-listed drugs dispensed irrespective of whether it attracted government reimbursement, removing the need to restrict to concessional beneficiaries. Future studies will undoubtedly benefit from this development and the facilitation of whole of population drug studies. We

did not compare access patterns between the Australian and Canadian populations; even the concessional Australian population was not directly comparable to the British Columbian income assistance population. We were unable to examine use of over-the-counter opioids or those available via private prescription or unsubsidised by the PBS or PharmaCare, thus it is likely our results underestimate total use and prescriber access patterns.

#### ***4.5 Conclusions***

The utility of pharmaceutical claims for the post-market surveillance of prescription drugs is increasingly recognised, and interrogation of these large databases represents a useful way of tracking potentially problematic prescribed opioid use. Our benchmarking approach has identified the utility of considering access patterns across the entire spectrum and across drug classes. These findings provide a first step toward an alternative method of quantifying problematic prescription drug use using routinely collected data.

## 4.6 References

1. Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet*. 2016; 387(10028): 1644-1656.
2. International Narcotics Control Board. Narcotic Drugs Technical Publications. 2004; [https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2004/Narcotics\\_2004\\_INCB\\_web.pdf](https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2004/Narcotics_2004_INCB_web.pdf). Accessed 20 January 2016.
3. International Narcotics Control Board. Narcotic Drugs Technical Publications. 2014; [https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2014/ND\\_TR\\_2014\\_4\\_Tables\\_EFS.pdf](https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2014/ND_TR_2014_4_Tables_EFS.pdf). Accessed 20 January 2016.
4. Blanch B, Pearson S, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *Br J Clin Pharmacol*. 2014; 78(5): 1159-1166.
5. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiol Drug Saf*. 2006; 15(9): 618-627.
6. Centers for Disease Control Prevention. CDC grand rounds: prescription drug overdoses-a US epidemic. *MMWR Morb Mortal Wkly Rep*. 2012; 61(1): 10-13.
7. Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, et al. Opioid epidemic in the United States. *Pain Physician*. 2012; 15(3 Suppl): ES9-38.
8. Kux L. Postmarketing requirements for the class-wide extended-release/long-acting opioid analgesics; public meeting; request for comments. *Fed Regist*. 2014; 79(77): 22499-22501.

9. Blanch B, Buckley NA, Mellish L, Dawson AH, Haber PS, et al. Harmonizing post-market surveillance of prescription drug misuse: a systematic review of observational studies using routinely collected data (2000–2013). *Drug Saf.* 2015; 38: 553-564.
10. Blanch B, Mellish L, Buckley N, Dawson A, Haber P, Pearson S. How is prescription opioid misuse measured, and what is the extent of opioid misuse globally? A systematic review of observational studies using routinely collected dispensing data (2000–2013). *Journal of Addictive Behaviors, Therapy & Rehabilitation.* 2014; in press.
11. Han H, Kass PH, Wilsey BL, Li C-S. Individual and county-level factors associated with use of multiple prescribers and multiple pharmacies to obtain opioid prescriptions in California. *PLoS One.* 2012; 7(9): e46246.
12. McDonald DC, Carlson KE. Estimating the prevalence of opioid diversion by "doctor shoppers" in the United States. *PLoS One.* 2013; 8(7): e69241.
13. Wilsey BL, Fishman SM, Gilson AM, Casamalhuapa C, Baxi H, et al. Profiling multiple provider prescribing of opioids, benzodiazepines, stimulants, and anorectics. *Drug Alcohol Depend.* 2010; 112(1-2): 99-106.
14. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA.* 2008; 300(22): 2613-2620.
15. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Res Notes.* 2015; 8(1): 634.

16. Government of British Columbia. PharmaCare for B.C. Residents.  
<http://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/about-pharmacare>. Accessed 27 January 2016.
17. Department of Health and Ageing. Trends in and drivers of Pharmaceutical Benefits Scheme expenditure. 2013; <http://www.pbs.gov.au/statistics/asm/2010/australian-statistics-on-medicine-2010.pdf>. Accessed 27 January 2016.
18. World Health Organization Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical Classification Structure and Principles. 2011; [http://www.whocc.no/atc/structure\\_and\\_principles/](http://www.whocc.no/atc/structure_and_principles/). Accessed 20 January 2016.
19. British Columbian Ministry of Social Development and Social Innovation. Employment and Assistance Regulations. 2015; <http://www.sdsi.gov.bc.ca/publicat/vol1/part3/3-3.htm#5>. Accessed 11 January 2016.
20. Baumblatt J, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, et al. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. *JAMA Intern Med*. 2014; 174(5): 796-801.
21. Gomes T, Mamdani MM, Dhalla IA, Cornish S, Paterson JM, Juurlink DN. The burden of premature opioid-related mortality. *Addiction*. 2014; 109(9): 1482-1488.
22. Jena AB, Goldman D, Weaver L, Karaca-Mandic P. Opioid prescribing by multiple providers in Medicare: retrospective observational study of insurance claims. *BMJ*. 2014; 348.
23. Kemp A, Paige E, Banks E. Beginner's guide to using pharmaceutical benefits scheme data: tips and pitfalls 2013;

[http://nceph.anu.edu.au/files/Guide\\_to\\_Using\\_PBS\\_Data\\_20131125.pdf](http://nceph.anu.edu.au/files/Guide_to_Using_PBS_Data_20131125.pdf). Accessed

17 March 2016.

24. Frauger E, Pauly V, Thirion X, Natali F, Pradel V, et al. Estimation of clonazepam abuse liability: a new method using a reimbursed drug database. *Int Clin Psychopharmacol*. 2009; 24(6): 318-324.
25. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, et al. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. *Pharmacoepidemiol Drug Saf*. 2004; 13(7): 473-481.
26. Pradel V, Frauger E, Thirion X, et al. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. *Pharmacoepidemiol Drug Saf*. 2009; 18(1): 36-43.
27. Blanch B, Buckley N, Srasuebkul P, Litchfield MJ, Pearson S. Prescription opioid use and potential misuse in Australia (2006-2013). *Pharmacoepidemiol Drug Saf*. 2015; 24: 157-158.
28. Shei A, Rice JB, Kirson NY, Bodnar K, Birnbaum HG, et al. Sources of prescription opioids among diagnosed opioid abusers. *Current Med Res Opin*. 2015; 31(4): 779-784.
29. Chen L-Y, Strain EC, Crum RM, Storr CL, Mojtabai R. Sources of nonmedically used prescription stimulants: differences in onset, recency and severity of misuse in a population-based study. *Drug Alcohol Depend*. 2014; 145: 106-112.
30. Green TC, Bowman SE, Ray M, Zaller N, Heimer R, et al. Collaboration or coercion? Partnering to divert prescription opioid medications. *J Urban Health*. 2013; 90(4): 758-767.

**Supplementary Table 4.1** Publically subsidised opioid analgesics and statins included in analysis by jurisdiction

Prescription drug (ATC code[s])	Australia	British Columbia
<i>Opioid analgesics</i>		
Buprenorphine (N02AE01)	✓	a
Codeine (N02AA59; N02AA79; R05DA04 <sup>b</sup> )	✓	✓
Dextropropoxyphene (N02AC04)	c	✓
Fentanyl (N02AB03)	✓	✓
Hydromorphone (N02AA03)	✓	✓
Methadone (N02AC)	✓	a
Morphine (N02AA01)	✓	✓
Oxycodone (N02AA05; N02AA55)	d	✓
Pentazocine (N02AD01)	c	✓
Pethidine (N02AB02)	c	✓
Tapentadol (N02AX06)	✓	✓
Tramadol (N02AX02, N02AX52)		
<i>Statins</i>		
Atorvastatin (C10AA05)	✓	✓
Fluvastatin (C10AA04)	✓	✓
Lovastatin (C10AA02)	d	✓
Pravastatin (C10AA03)	✓	✓
Rosuvastatin (C10AA07)	✓	✓
Simvastatin (C10AA01)	✓	✓

<sup>a</sup> Unable to distinguish between use for pain or opiate maintenance treatment

<sup>b</sup> Codeine dispensed under this Anatomical Therapeutic Chemical (ATC) classification code may be dispensed for the indication of cough suppression or pain

<sup>c</sup> Not PBS-listed in Australia in 2011

<sup>d</sup> Not available via prescription in Australia

**Supplementary Table 4.2** Distribution of number of unique statin or opioid prescribers in Australia and British Columbia (2011)

	<b>Australia<sup>a,b</sup></b>		<b>British Columbia (all)</b>		<b>British Columbia (income assistance)</b>	
<b>Number of unique prescribers</b>	<b>Opioid cohort N = 118 125 N (%)</b>	<b>Statin cohort N = 147 728 N (%)</b>	<b>Opioid cohort N = 482 591 N (%)</b>	<b>Statin cohort N = 397 345 N (%)</b>	<b>Opioid cohort N = 50 633 N (%)</b>	<b>Statin cohort N = 21 267 N (%)</b>
<b>Median (range)</b>	<b>1 (1-81)</b>	<b>1 (1-9)</b>	<b>1 (1-45)</b>	<b>1 (1-12)</b>	<b>1 (1-45)</b>	<b>1 (1-11)</b>
<i>For 1-3 prescriber(s) descriptive statistics see Table 4.3</i>						
<b>4 prescribers</b>	3 737 (3.2)	1 565 (1.1)	10 393 (2.2)	5 371 (1.4)	2 983 (5.9)	689 (3.2)
<b>5 prescribers</b>	1 734 (1.5)	263 (0.2)	4 567 (1.0)	1 061 (0.3)	1 627 (3.2)	229 (1.1)
<b>6 prescribers</b>	848 (0.7)	64 (0.0)	2 218 (0.5)	228 (0.1)	904 (1.8)	69 (0.3)
<b>7 prescribers</b>	494 (0.4)	<60 (0.0)	1 230 (0.3)	56 (0.0)	579 (1.1)	32 (0.2)
<b>8 prescribers</b>	273 (0.2)	<60 (0.0)	710 (0.2)	18 (0.0)	356 (0.7)	12 (0.1)
<b>9 prescribers</b>	168 (0.1)	<60 (0.0)	419 (0.1)	9 (0.0)	235 (0.5)	5 (0.0)
<b>10 prescribers</b>	123 (0.1)	<60 (0.0)	278 (0.1)	7 (0.0)	158 (0.3)	7 (0.0)
<b>11 prescribers</b>	73 (0.1)	<60 (0.0)	206 (0.0)	1 (0.0)	124 (0.2)	1 (0.0)
<b>12 prescribers</b>	64 (0.1)	<60 (0.0)	125 (0.0)	1 (0.0)	81 (0.2)	0 (0.0)
<b>13 prescribers</b>	<60 (0.0)	<60 (0.0)	74 (0.0)	0 (0.0)	53 (0.1)	0 (0.0)
<b>14 prescribers</b>	<60 (0.0)	<60 (0.0)	62 (0.0)	0 (0.0)	38 (0.1)	0 (0.0)
<b>15 prescribers</b>	<60 (0.0)	<60 (0.0)	53 (0.0)	0 (0.0)	31 (0.1)	0 (0.0)
<b>16 prescribers</b>	<60 (0.0)	<60 (0.0)	31 (0.0)	0 (0.0)	20 (0.0)	0 (0.0)
<b>17 prescribers</b>	<60 (0.0)	<60 (0.0)	22 (0.0)	0 (0.0)	13 (0.0)	0 (0.0)

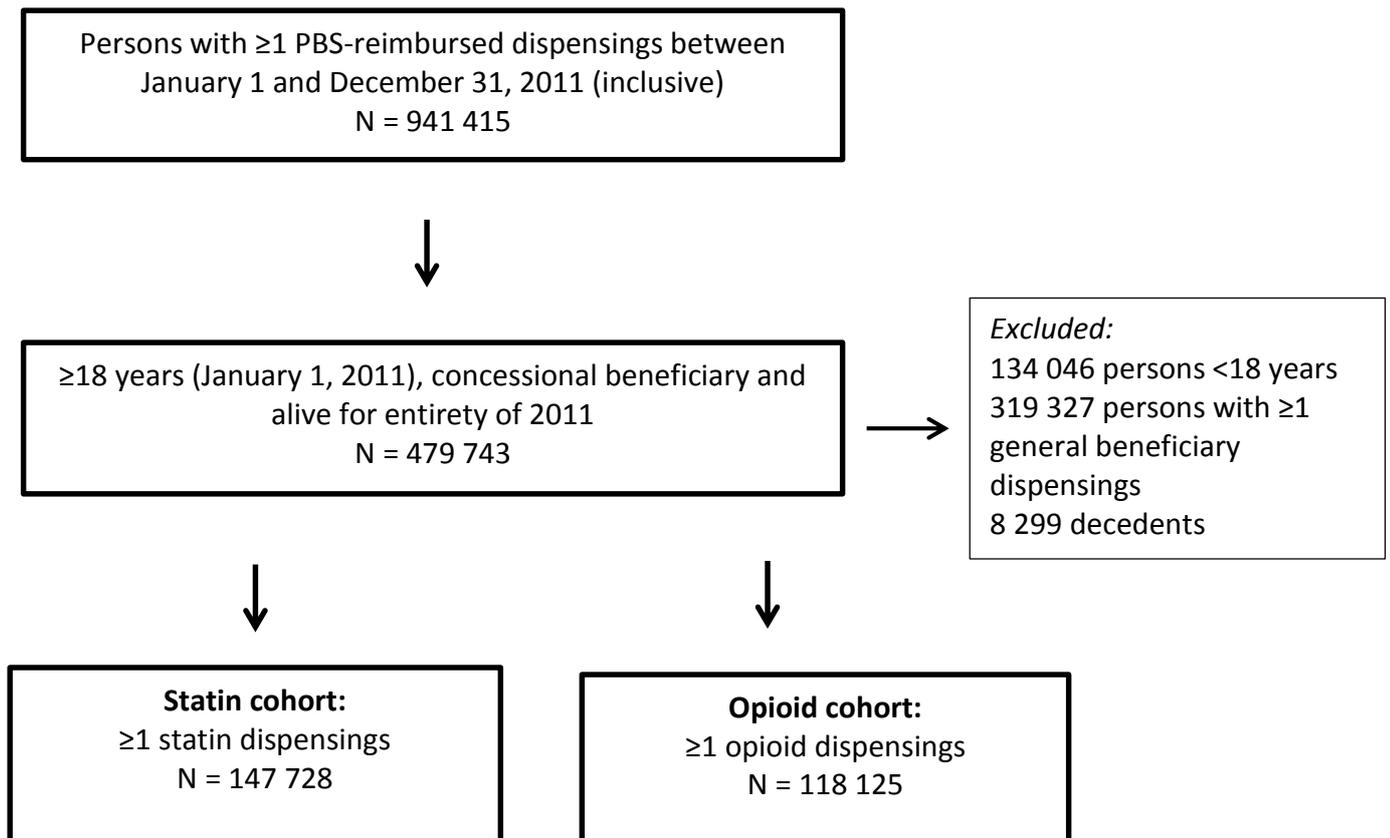
<b>18 prescribers</b>	<60 (0.0)	<60 (0.0)	23 (0.0)	0 (0.0)	16 (0.0)	0 (0.0)
<b>19 prescribers</b>	<60 (0.0)	<60 (0.0)	20 (0.0)	0 (0.0)	14 (0.0)	0 (0.0)
<b>≥20 prescribers</b>	<60 (0.0)	<60 (0.0)	50 (0.0)	0 (0.0)	27 (0.1)	0 (0.0)

---

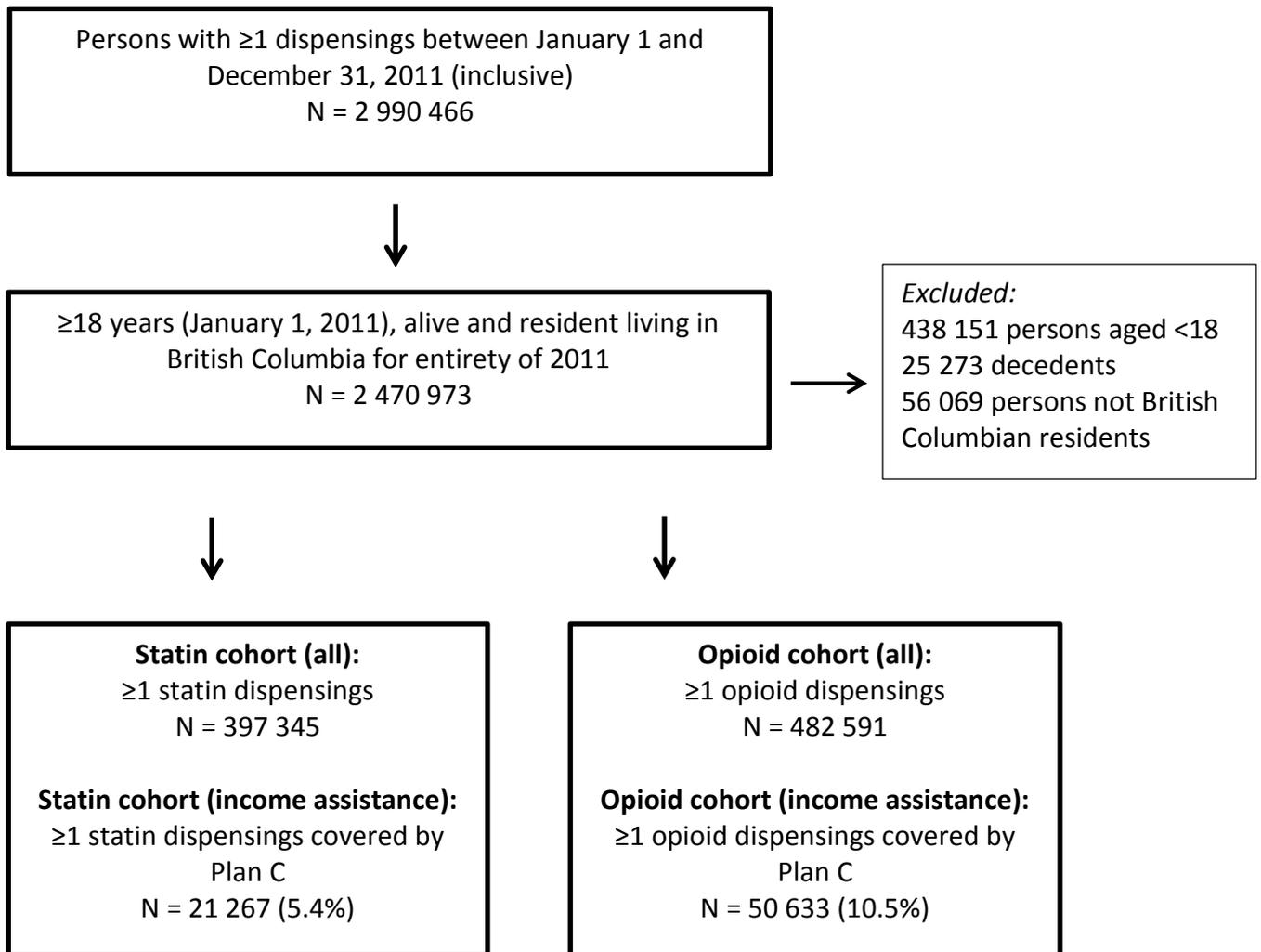
<sup>a</sup> Australian concessional beneficiaries only

<sup>b</sup> Due to our Australian data agreement, we are unable to report cell sizes pertaining to <60 persons

**Supplementary Figure 4.1A** Australian cohort inclusion criteria

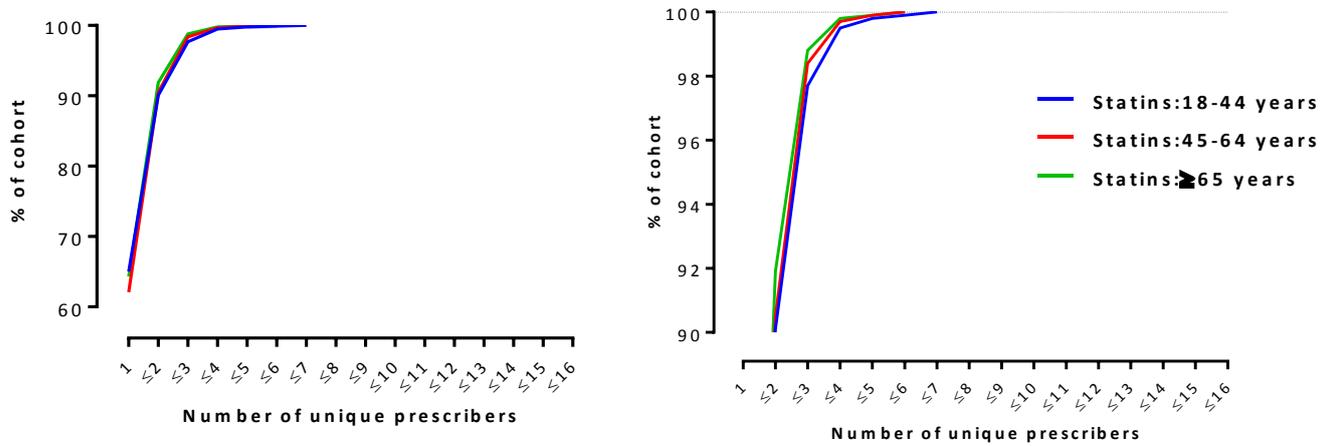


**Supplementary Figure 4.1B** British Columbian cohort inclusion criteria

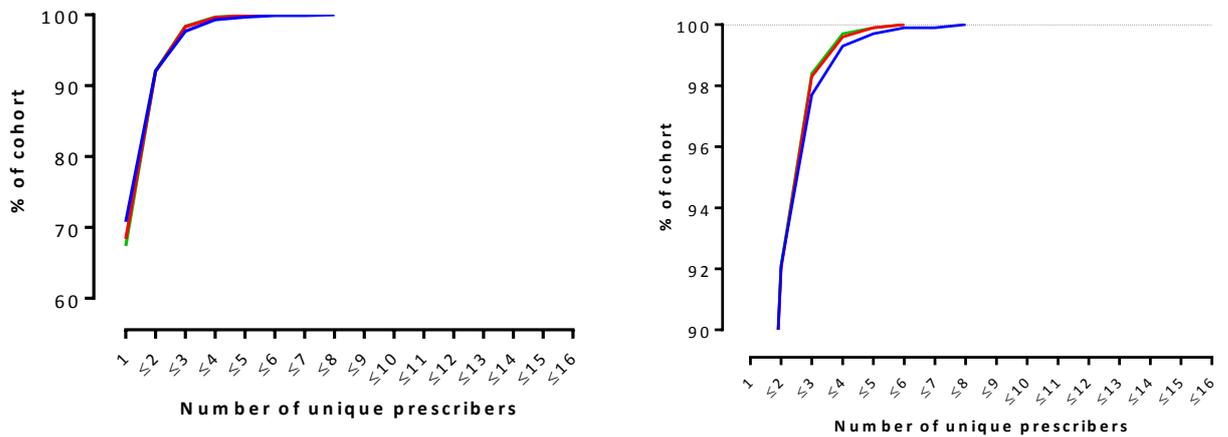


**Supplementary Figure 4.2** Cumulative frequency of unique statin prescribers by age group

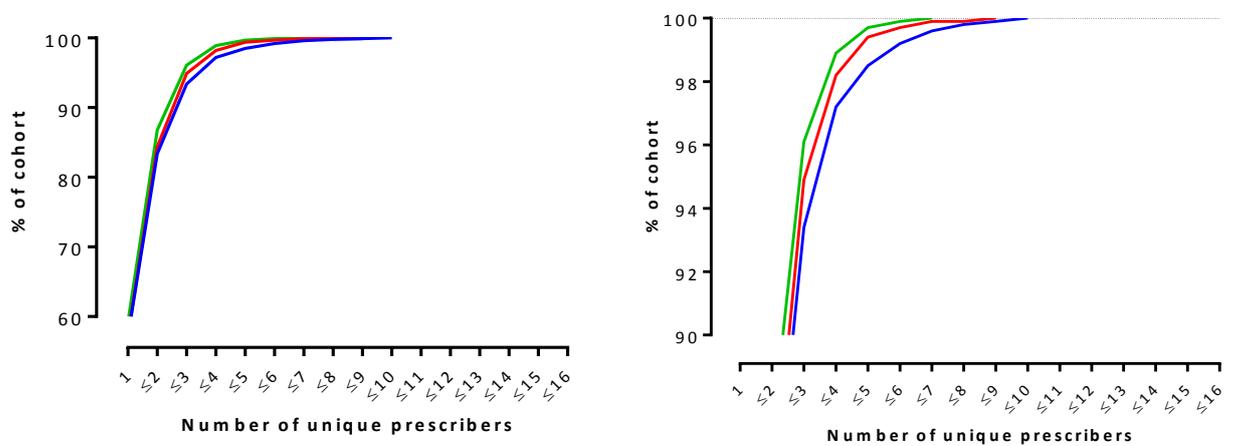
4.2A Australian concessional beneficiaries: entire spectrum (left); upper decile (right)



4.2B British Columbia (all): entire spectrum (left); upper decile (right)



4.2C British Columbia (income assistance): entire spectrum (left); upper decile (right)



## ***Chapter Five: The POPPY research program protocol: investigating opioid utilisation, costs and patterns of extramedical use in Australia***

In Chapter Four we present the results of the first cross-jurisdictional study examining whole-of-population prescription drug access patterns across drug classes. We demonstrate statins and opioids are accessed similarly across two jurisdictions with similar healthcare arrangements; albeit a higher proportion of opioid users access  $\geq 4$  prescribers. We also found specific patient factors are associated with higher prescriber access patterns including younger age and persons receiving income assistance. In Chapter Six we focus on several patient factors associated with increasing opioid access patterns across multiple metrics commonly used to define misuse. This chapter contains the POPPY project protocol to provide background information for the pharmaceutical data analysed in Chapter Six.

This chapter is a reproduction of the following publication:

Louisa Degenhardt, Bianca Blanch, Natasa Gisev, Briony Laranca, Sallie-Anne Pearson. The POPPY Research Programme protocol: investigating opioid utilisation, costs and patterns of extramedical use in Australia. *BMJ Open*. 2014; 4: e007030.

Formatting note: To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. The key points and abstract are formatted according to the *BMJ Open* style guide. We provide the reference list at the end of each chapter. Supplementary materials are provided after the reference list for this chapter.

## **Key Points**

### *Strengths and limitations of this study*

- Using data on prescriptions reimbursed by the Pharmaceutical Benefits Scheme (PBS), this study will provide novel data on the patterns and costs of opioid use, including extramedical use, in the Australian population. This will provide the most detailed information to date regarding person-level patterns of opioid consumption in Australia.
- The research program is limited by:
  - The extent to which these data reflect total opioid consumption. PBS data do not include private prescriptions or over-the-counter opioids. In addition, parts of the study will not capture low-cost PBS-listed items dispensed to Australians with the highest patient copayment threshold.
  - Dispensing claims do not detail clinical information, including indication for use, which poses challenges given doses for opioids vary depending on the nature of the pain being managed. However, by using complete PBS dispensing history for each individual, we will be able to identify patients with a recent cancer treatment history.
  - The absence of gold-standard proxy indicators of extramedical opioid use. As such, we will develop indicators through consultation of the literature and feedback from expert clinicians in the fields of pain, cancer and addiction. Sensitivity analyses will be used to establish whether our conclusions are affected by variations in definitions.

## ***Abstract***

### *Introduction*

Opioid prescribing is increasing in many countries. In Australia, there is limited research on patterns of prescribing and access, or the outcomes associated with opioid use. The aim of this research program is to use national dispensing data to estimate opioid use and costs, including problematic or extramedical use in the Australian population.

### *Methods and analysis*

In a cohort of persons dispensed at least one opioid in 2013, we will estimate monthly utilisation and costs of prescribed opioids, overall and according to individual opioid formulations and strengths. In a cohort of new opioid users, commencing therapy between 1 July 2009 and 31 December 2013, we will examine patterns of opioid use including initiation of therapy, duration of treatment and concomitant use of opioids and other prescribed drugs. We will also examine patterns of extramedical opioid use based on indicators including excess dosing, use of multiple opioids concomitantly, doctor/ pharmacy shopping and accelerated time to prescription refill.

### *Ethics and dissemination*

This protocol was approved by the NSW Population and Health Services Research Ethics Committee (March 2014) and data access was approved by the Australian Government Department of Human Services External Review Evaluation Committee (June 2014). This will be one of the first comprehensive Australian studies with the capability to investigate individual patterns of opioid use and track extramedical use. In the first instance our analysis will be based on 4.5 years of dispensing data but will be expanded with ongoing annual data

updates. This research has the capability to contribute significantly to pharmaceutical policy within Australia and globally. In particular, the trajectory of extramedical prescription opioid use has been the subject of limited Australian research to date. The results of this research will be published widely in general medical, pharmacoepidemiology, pain, addiction and psychiatry journals.

## **5.1 Introduction**

The global increase in prescribed opioid use over the past 30 years has been well documented.<sup>1–8</sup> In Australia, between 1992 and 2007, there was a 300% increase in the number of opioid dispensings in the community.<sup>5</sup> In 2012, 7.4 million opioid prescriptions were dispensed via the Australian Pharmaceutical Benefits Scheme (PBS), costing the Australian government approximately AU\$271 million. In the 20-year period 1992–2012, the Commonwealth of Australia subsidised over AU\$2 billion in prescribed opioids, with oxycodone and morphine accounting for AU\$1.1 billion.<sup>9</sup> Europe and the USA have seen even larger increases in opioid dispensings than Australia.<sup>10</sup> Despite the Australian government's significant investment in these prescription drugs, we know little about the way they are used in routine clinical care.

The observed global increase in opioid use can be attributed, in part, to the broadening of regulatory and subsidy approval of opioids to manage chronic noncancer pain; previously use was restricted to the management of cancer pain. As opioid use has increased, so too has the concern from healthcare professionals and the public in relation to the harms of prolonged medical use, including concerns about the appropriateness of prescribing opioids long term and the risk of iatrogenic dependence.<sup>11</sup> The most serious risk associated with opioid use is the harm related to opioid overdose. In the USA, prescribed drugs account for more fatal and non-fatal overdoses than illicit drugs.<sup>12</sup> People dying from opioid overdoses often use other prescription drugs concomitantly such as benzodiazepines, antidepressants, antipsychotics and psychostimulants,<sup>13,14</sup> which may further contribute to the risk of an adverse outcome. In Australia, notable increases in reported opioid dispensings have occurred.<sup>5</sup> This has been associated with hospital separations for opioid poisoning,

treatment episodes<sup>3,9</sup> and deaths attributed to pharmaceutical opioids such as oxycodone.<sup>4,15</sup>

‘Extramedical use’ is defined as use not as directed by a doctor.<sup>16</sup> Among other things, it may include using more than directed by the doctor; asking for escalating doses; obtaining prescriptions from multiple doctors without their knowledge; tampering with opioids and taking opioids via routes other than intended (e.g. snorting or injecting).<sup>16</sup> A 2010 Australian national survey reported a 7.4% lifetime prevalence and 4.2% 12-month prevalence of using prescription drugs such as analgesics, sedatives/hypnotics, methadone, other opioids and steroids when not medically indicated,<sup>17</sup> equating to approximately 1 in 14 Australians engaging in extramedical use of a prescribed drug in their lifetime (with a higher prevalence in younger age groups).

Observational cohort studies from the USA and Europe have examined the natural history of opioid analgesic use for chronic non-cancer pain.<sup>18</sup> Small retrospective cohort studies have examined treatment duration, pain reduction, adverse drug events<sup>19</sup> and aberrant behaviours.<sup>20</sup> Larger retrospective cohort studies have examined the risk of overdose,<sup>21</sup> the impact on disability,<sup>22</sup> non-medical use,<sup>23</sup> conditions treated in older adults,<sup>24</sup> and rates of adverse events.<sup>25</sup>

However, in Australia, few studies have examined person-level behaviours of people prescribed opioids, prescribing patterns, patterns of use, or the outcomes and costs associated with this use.<sup>26–28</sup> In order to gain a comprehensive understanding of these issues, we started a program of research examining the patterns and costs of PBS-subsidised

opioid use, including extramedical use in the Australian population. This protocol summarises the scope of our program.

The overall objective of this research program is to evaluate the patterns and costs of opioid use in Australia. Specifically, we aim to:

1. Estimate monthly and annual utilisation and costs of prescribed opioids, overall and according to individual opioid formulations and strengths.
2. Examine patterns of opioid use including initiation of therapy, duration of treatment, concomitant use of opioids and other therapy.
3. Examine patterns of extramedical opioid use based on indicators including excess dosing, use of multiple opioids concomitantly, doctor/pharmacy shopping, and accelerated time to prescription refill.

## **5.2 Methods**

### *5.2.1 Setting*

Australia has a publically funded universal healthcare system entitling all Australian citizens and permanent residents to a range of subsidised health services. This includes free treatment in public hospitals (funded jointly by Commonwealth and State/Territory governments), subsidised outpatient services including consultations with medical and selected healthcare professionals (funded by the Commonwealth's Medicare Benefits Scheme) and drugs dispensed in the community and private hospitals (funded by the PBS). Drugs prescribed to public hospital inpatients are covered primarily by hospital budgets.

### *5.2.2 Opioids of interest*

The prescribed opioids of interest in this study include drugs belonging to the World Health Organization's Anatomical Therapeutic Chemical classification system

(<http://www.who.int/classifications/atcddd/en/>) categories N02A, N07B and R05D (Table 5.1). We requested data for all formulations and strengths of these drugs (individual PBS item numbers). Methadone or buprenorphine may be prescribed for the indication of opiate maintenance therapy or pain. For the indication of opiate maintenance therapy, these drugs are listed under the S100 Highly Specialised Drugs Program (S100 HSDP) administered by individual Australian States and Territories rather than under the national funding system. We listed these indications for completeness, however, the Australian Government Department of Human Services (DHS) do not record dispensings for opioids dispensed under the state-based S100 HSDP. All opioid dispensing records we obtain will be for the indication of pain.

### *5.2.3 Data of interest*

Our research program will be underpinned by access to dispensing claims processed by the DHS, the PBS administering body. Until recently, DHS only recorded dispensing claims attracting a PBS-subsidy. As such, drug dispensings costing less than the patient copayment threshold were not ascertained in the collection. In effect, low-cost drugs dispensed to beneficiaries with the highest patient copayment threshold (referred to as general beneficiaries) have been under-ascertained; this issue does not impact on drugs dispensed to beneficiaries with lower copayment thresholds (PBS concessional beneficiaries). In April 2012, DHS began recording under-copayment dispensings.

**Table 5.1** Opioids of interest<sup>a</sup>

<b>Drug</b>	<b>ATC code(s)<sup>b</sup></b>
Buprenorphine	N02AE01, N07BC01, N07BC51
Codeine	N02BE51, N02AA59, R05DA04 <sup>c</sup>
Fentanyl	N02AB03
Hydromorphone	N02AA03
Methadone	N02AC52, N07BC02
Morphine	N02AA01
Oxycodone	N02AA05, N02AA55
Tapentadol	N02AX06
Tramadol	N02AX02

ATC: Anatomical Therapeutic Chemical; PBS: Australian Pharmaceutical Benefits Scheme; WHO: World Health Organisation

<sup>a</sup> Tapentadol PBS-subsidised from 2014

<sup>b</sup> ATC classification system is an internationally established methodology endorsed by the WHO that is used to classify drugs based on the organ or system on which they act, or their therapeutic and chemical characteristics. Details of the ATC classification system are found online at:

<http://www.who.int/classifications/atcddd/en/>.

<sup>c</sup> Single ingredient codeine 30 mg tablets (opium alkaloids and derivatives) are ATC coded to the respiratory system R05D and not the nervous system N02A.

Our PBS-data requests were structured in two parts as described below:

- *Prevalent user cohort:* comprising Australians dispensed at least one opioid. This is a national cohort of all persons (of any age) prescribed at least one opioid of interest in a given calendar year (with the first year of data being 2013). The cohort will provide contemporary information about the prevalence of monthly and annual prescribed opioid use across the Australian population, including data from under-copayment opioid prescriptions. Data will be updated annually.
- *Incident user cohort:* comprising Australians starting new opioid therapy. This is a national cohort focusing on persons dispensed at least one opioid in the period 1 July 2009 to 31 December 2013 inclusive. Our observation period was chosen as the DHS holds PBS data for a period of only 4 years and 6 months. These data are updated daily and when each additional day is added, the earliest date in the data set is deleted. Therefore, our exact study period is dependent on the date of extraction. This cohort will be used to examine patterns of prescribed opioid use, including extramedical use. Inclusion criteria are as follows: (1) opioid naïve for at least 90-days prior to the index prescription (see Supplementary Material 5.1 for details on the way in which this was operationalised); (2) aged  $\geq 18$  years at the index prescription. We chose a 90-day wash-out period for cohort inclusion because it was considered sufficient time to ensure that any new, index prescriptions reflected a new 'course' of treatment for a new or recurrent indication. It is possible that some individuals will receive a new prescription under this definition for an indication for which they have been treated previously. However, we will also undertake sensitivity analyses by extending the period of non-use to 180-days. This cohort will also be

updated annually. Tables 5.2 and 5.3 detail the variables requested from DHS for the prevalent and incident user cohorts.

#### *5.2.4 Statistical analysis*

We will use best-practice pharmacoepidemiological methods to explore prescribed opioid use in the two cohorts. The general approaches are detailed below:

*Utilisation and costs:* we will estimate the monthly and annual prevalence and costs of opioid use overall and according to individual opioid formulations and strengths. Utilisation estimates will be based on number of prescriptions, defined daily dose (DDD)/1000 population per day or in oral morphine equivalent mg.<sup>29</sup> Analyses will be stratified according to patient age, sex, location of residence and indices of socioeconomic disadvantage. Data from the Australian Bureau of Statistics will determine population estimates for each subgroup of interest. Estimates will also be presented using ESRI ArcGIS (a mapping software program). This will show overall national patterns of use by geographical area of patient, prescriber or dispensing pharmacy (e.g. Statistical Local Area, jurisdictionally), as well as graphical presentation of variations in levels of use. Publically available data on the demographic characteristics of geographical areas will be obtained from the Australian Bureau of Statistics (e.g. age distribution, income, education and unemployment).

1. *Patterns of opioid use:* we will examine patterns of use in the following ways:
  - A. Median duration of opioid treatment: defined as the time from the first opioid dispensing record to the last dispensing record plus 30 days. These estimates can also detail different courses of opioid therapy by accounting for breaks in treatment of more than 60 days.

**Table 5.2** Variables requested regarding cohort demographics

<b>Variables</b>	<b>Justification</b>
Scrambled patient ID	A unique sequence number enabling person-level analysis and linkage to PBS dataset
Month and year of birth (mm/yy)	To report demographics of cohort and used to stratify analyses according to age group
Sex	To report demographics of cohort and used to stratify analyses according to sex
Month and year of death (mm/yy)	To censor the follow-up time for each individual in the cohort
Postcode of residence mapped to SLA	Used to identify location of residence and map to indices of socioeconomic disadvantage (i.e. the <i>Socio-Economic Indexes for Areas</i> [SEIFA] <sup>a</sup> ) and remoteness (i.e. the <i>Accessibility/Remoteness Index of Australia</i> [ARIA] <sup>b</sup> ).
Geographic location of residence according to the SA2	Used to identify geographic location of residence and map to SEIFA and ARIA classifications.

ABS: Australian Bureau of Statistics; ARIA: Accessibility/Remoteness Index of Australia; PBS: Australian Pharmaceutical Benefits Scheme; SA2: Statistical Area Level 2; SLA: Statistical Local Area

<sup>a</sup> SEIFA is a product developed by the ABS that ranks areas in Australia according to relative socioeconomic advantage and disadvantage. The indexes are based on information from the 5-yearly census. Details can be found at:

<http://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa>.

<sup>b</sup> The ABS' Remoteness Areas classification include 'major cities', 'inner regional', 'outer regional', 'remote' and 'very remote'. Details have been reported elsewhere.<sup>54,55</sup>

**Table 5.3** Australian Pharmaceutical Benefits Scheme data on opioid dispensing (and other drug dispensing) history

<b>Variables</b>	<b>Description</b>	<b>Justification</b>
Scrambled patient ID	A unique sequence number	Enable person-level analysis and linkage to sociodemographic dataset
Month and year of birth	Month and year when each person was born	Determine age at time of dispensing. Also used as a cross-check with data in demographic file
Sex	Patient sex	Cross-check with data in demographic file
Date of supply	Date drug is dispensed	Establish temporal relationship in dispensing records
Item code	A unique number which represents the dose, form and strength of the pharmaceutical item patients are dispensed	Identify drugs of different forms and strengths
ATC code	Anatomical Therapeutic Chemical classification code	Delineate between drug types
Generic name	Generic drug name	Delineate between drug types
Quantity dispensed	Quantity of drug dispensed	Calculate defined daily dose and durations of treatment
Original or repeat prescription	A variable to distinguish between repeat or new prescriptions	Understand pattern of treatment
Beneficiary level	General beneficiary $\pm$ safety net; concession card holder $\pm$ safety net	Identify level of entitlement and determine comprehensiveness of data capture
PBS benefit	Amount paid by the Australian government	Determine the total cost incurred by the Australian government to supply opioids in a given calendar year
Prescriber scrambled ID	A unique sequence number given to each prescriber	Delineate between prescriptions written by different doctors
Prescriber location	Postcode mapped to SLA	Establish location of practice
Prescriber type	Identifies primary specialty of the prescribing doctor	Identify what type of doctors prescribe drugs of interest
Pharmacy scrambled ID	A unique sequence number given to each dispensing pharmacy	Delineate between prescriptions dispensed at different pharmacies
Pharmacy location	Postcode mapped to SLA	Establish location of pharmacy

ID: identifier; SLA: Statistical Local Area

- B. Dose escalation: we will estimate the average daily dose of each opioid dispensing using the internationally recognised DDD unit.<sup>30</sup> At the individual level, we will calculate the changes in average DDDs by prescription and report the number of patients in whom doses are increasing, and by what level, over time.
- C. Concomitant opioid and other concomitant drug use: we will investigate the concomitant use of multiple opioids, in addition to the use of opioids with other prescribed drugs, such as benzodiazepines, antidepressants and antipsychotics. Concomitant use will generally be defined as the observation of at least two dispensing records from different drugs within a specific time frame. The rules will vary according to the therapy of interest. Furthermore, we will identify individuals at risk of potentially harmful drug–drug interactions deemed to be clinically relevant in the literature and common drug information resources.<sup>31–33</sup> These will be examined using a previously published approach<sup>34</sup> overall, and for specific population subgroups such as older adults.
2. *Extramedical use*: indicators of extramedical opioid use —we will adopt measures of extramedical use described previously in the literature<sup>16</sup> and report on the rates of these patterns of extramedical use:
- A. Excess dosing: defined as average daily dosing outside guideline recommendations.<sup>35–37</sup>
- B. Concomitant opioid use: as described above.<sup>36,38</sup>
- C. Doctor shopping: opioid prescriptions written by more than one doctor and dispensed within a specific time frame.<sup>14,39–45</sup>

- D. Pharmacy shopping: opioid dispensings from more than one pharmacy within a specified time frame.<sup>40–44</sup>
- E. Accelerated prescription refill: repeated dispensing of opioid prescriptions earlier than the estimate of when the prescription is complete.<sup>36,37,46–49</sup> The drug possession ratio and refill compliance rate are measures which use administrative data to assess drug adherence. We have included accelerated prescription refill as one of our measures of extramedical use.

We may restrict some of our analyses to concessional beneficiaries (persons receiving a government pension), as not all prescription opioids of interest are above the general beneficiary copayment amount. Other drugs of interest including psychotropic drugs such as antidepressants, antipsychotics, benzodiazepines and central nervous system stimulants, also fall below the general beneficiary copayment. We will also undertake analyses with and without persons dispensed drugs for cancer treatment to establish how the inclusion of patients with cancer (who generally receive significantly higher opioid doses than patients without cancer) impact on our estimates.

#### *5.2.5 Data access approval*

Data access has been approved by the DHS External Review Evaluation Committee (MI0166). However, DHS have recently advised that it may be necessary to restrict our cohorts due to the considerable amount of data they will be required to provide to us. For example, to access the entire dispensing history of all people dispensed an opioid in our incident user cohort, it has been estimated that we would be provided with 40% of the

entire DHS data holdings. As such, our cohorts may be restricted to a 10% random sample of the national opioid user cohort.

#### *5.2.6 Consent and privacy considerations*

*Use and disclosure of information:* Commonwealth data are governed under the Privacy Act 1988. Information Privacy Principle (IPP) 2 under the Privacy Act 1988 provides that personal information should not be used or disclosed for any purpose other than the primary purpose of the collection. We have obtained approval for the use of data for a secondary purpose: that of research involving access to person-level information. Under IPP2.1(d), use or disclosure for another purpose is allowed if (A) it is necessary for research and it is impracticable to gain consent AND (B) the use is in accordance with Section 95A guidelines (which provides a process to resolve the conflict that may arise between the public interest in privacy and the public interest in medical research).

*Consent:* The waiver for individual consent was approved by the Population and Health Services Research Ethics Committee in accordance with Section 95A of the Commonwealth Privacy Act 1988. This was because:

- There were hundreds of thousands of people in the cohort, so it was not possible or practical to obtain consent because of the large study population.
- Obtaining consent would prejudice the scientific value of the research due to the high participation rates required for unbiased samples (at least 90%),<sup>50</sup> and the Australian evidence about the sociodemographic differences between participants who consent to data linkage research and those who do not.<sup>51</sup>

- We believe the public interest in this research outweighs the public interest in privacy protection. We consider the benefits to be great and the risk to be small. Currently we know little about the way in which opioids are used in the real world marketplace. Our research has the potential to address key issues such as the risks and benefits of prescribing opioids in Australia. These findings are likely to have national and global significance.

We have minimised the risk to personal privacy by ensuring:

- Only researchers involved in data analysis will have access to the data.
- Data will be securely stored at both sites (see below).
- The research team will not be in possession of any personally identifying information. The files released to the research team will not contain patients' name, rather a unique patient number will be generated by the DHS staff.

Finally, all data will be presented in aggregated form only and potentially identifiable information will not be published. We will suppress data with small cell sizes.

#### *5.2.7 Confidentiality of data and record retention*

This is a collaborative project involving two research teams, one based at the National Drug and Alcohol Research Centre, The University of New South Wales, Australia, and one based at the Faculty of Pharmacy, The University of Sydney, Australia. To ensure consistency between analyses and research teams, decision rules will be developed in group meetings and all analyses will be conducted in Statistical Analysis Software (SAS) so all relevant code

can easily be shared where necessary. The confidentiality of records will be ensured by strict adherence to the study protocol in relation to access to, transfer and storage of study data.

### **5.3 Discussion**

The rate of pharmaceutical opioid use is increasing across the globe. However, the actual extent of such use and extramedical use, is currently unknown. The research program outlined in this protocol will be the first large-scale and nationally representative Australian study to examine patterns of opioid use, including extramedical use, and the costs associated with this use. Previously, PBS opioid dispensing data has typically been analysed using aggregated data.<sup>5,9</sup> This research will also form the foundation of additional studies that can examine the medical consequences of excessive prescription opioid use. This type of research will be possible by access to emergency department and hospitalisation plus cause of death data.

From a clinical perspective, we will investigate common opioid utilisation patterns and identify behaviour indicative of extramedical use of opioids. Furthermore, we will investigate the prevalence of potentially inappropriate combinations of drugs prescribed with opioids, estimating the number of individuals at risk of adverse drug events due to potentially harmful drug–drug interactions. Together, this information could provide a strong evidence base for targeted future intervention program to identify and treat high-risk individuals across Australia, as well as form the basis of developing appropriate harm reduction strategies.

From a public health perspective, this research program will serve as an important first step to understanding and monitoring prescription opioid use, costs and extramedical use of opioids, now and into the future. Regulators across jurisdictions currently use different criteria for authorising long-term opioid therapy, identifying at-risk patients and measuring potentially problematic opioid use. Valid indicators are required to identify the emergence of problems and provide information that will allow the extent of the problem to be monitored. Therefore, through the development of robust proxies or indicators of extramedical opioid use, this study will yield a useful surveillance tool for public health authorities. Currently no universally accepted indicators exist,<sup>52</sup> and given the growing problem of opioid use in Australia and globally, the indicators have many potentially useful future applications.

### *5.3.1 Limitations*

It is important to acknowledge several limitations of these data. The first relates to the extent to which these data reflect total opioid consumption in Australia. As noted earlier, until 2012 only drug dispensings reimbursed under the PBS appear in PBS data. Therefore, drug dispensings costing less than the general beneficiary contribution that did not attract a PBS-subsidy are not captured in these data. This is particularly problematic for selected opioids. Private prescriptions are also not included in the PBS collection, which account for an unknown but potentially substantial number of opioid prescriptions in Australia. Finally, these data do not include opioids that are available in pharmacies without a prescription (over-the-counter opioids), which in Australia includes codeine, the unit sales of which were more than 15 million in 2013 (personal communication, Gisev N, Nielsen S, Bruno R, et al, 2014). Notwithstanding these limitations, these data certainly comprise the most detailed

information to hand about person-level patterns of opioid consumption in Australia, permitting detailed estimates of clinical issues that are of increasing community concern and great public health importance.

Second, dispensing claims do not detail clinical information, particularly relating to indication for use. This poses particular challenges given opioids are prescribed at different doses depending on the nature of the pain being managed; dosing for cancer and non-cancer pain are likely to differ significantly. Given we will be provided with the PBS-dispensing history of all persons undergoing opioid treatment, we have the capacity to undertake sensitivity analyses excluding patients with a history of cancer treatment. However, this approach will not be definitive as cancer drug dispensing history is likely to be a specific but not sensitive proxy for a cancer diagnosis.

The final limitation relates to the extent to which indicators of extramedical use accurately reflect the problem. We will develop our proxies through a process of consultation of the extant literature,<sup>53</sup> and ongoing discussion with and feedback from expert clinicians in the fields of pain, cancer and addiction. We will make ongoing efforts to generate valid indicators to the fullest extent possible. Our use of sensitivity analyses to check whether our conclusions are affected by variations in definitions will also be a feature of our analyses.

#### ***5.4 Conclusions***

This is a novel Australian research program of opioid use, costs and extramedical use at an individual level, with ongoing updates over time. This research has the capability to contribute significantly to pharmaceutical policy within Australia and globally.

## 5.5 References

1. Bell JR. Australian trends in opioid prescribing for chronic non-cancer pain, 1986–1996. *Med J Aust.* 1997; 167(1): 26–29.
2. Berbatis CG, Sunderland VB, Bulsara M, Lintzeris N. Trends in licit opioid use in Australia, 1984–1998: comparative analysis of international and jurisdictional data. *Med J Aust.* 2000; 173(10): 524–527.
3. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. *Med J Aust.* 2011; 195(5): 280–284.
4. Roxburgh A, Burns L, Drummer OH, Pilgrim J, Farrell M, et al. Trends in fentanyl prescriptions and fentanyl-related mortality in Australia. *Drug Alcohol Rev.* 2013; 32(2): 269–275.
5. Leong M, Murnion B, Haber P. Examination of opioid prescribing in Australia from 1992 to 2007. *Intern Med J.* 2009; 39(10): 676–681.
6. Hudec R, Tisonova J, Bozekova L, Foltan V. Trends in consumption of opioid analgesics in Slovak Republic during 1998–2002. *Eur J Clin Pharmacol.* 2004; 60(6): 445–448.
7. Garcia del Pozo J, Carvajal A, Vilorio JM, Velasco A, Garcia del Pozo V. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *Eur J Clin Pharmacol.* 2008; 64(4): 411–415.
8. Eisenberg E, Adler R. Consumption of opioids in a hospital setting— what can we learn from a 10 year follow-up? *Isr Med Assoc J.* 2004; 6(1): 19–23.
9. Blanch B, Pearson S, Haber P. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *Br J Clin Pharmacol.* 2014; 78(5): 1159–1166.

10. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ*. 2009; 181(12): 891–896.
11. Compton WM, Volkow ND. Abuse of prescription drugs and the risk of addiction. *Drug Alcohol Depend*. 2006; 83(Suppl 1): S4–7.
12. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend*. 2006; 81(2): 103–107.
13. Rintoul AC, Dobbin M, Nielsen S, Degenhardt L, Drummer OH. Recent increase in detection of alprazolam in Victorian heroin-related deaths. *Med J Aust*. 2013; 198(4): 206–209.
14. Martyres RF, Clode D, Burns JM. Seeking drugs or seeking help? Escalating “doctor shopping” by young heroin users before fatal overdose. *Med J Aust*. 2004; 180(5): 211–214.
15. Rintoul AC, Dobbin MD, Drummer OH, Ozanne-Smith J. Increasing deaths involving oxycodone, Victoria, Australia, 2000–09. *Inj Prev*. 2011; 17(4): 254–259.
16. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick R. Definitions related to the use of pharmaceutical opioids: extramedical use, diversion, non-adherence and aberrant medication-related behaviours. *Drug Alcohol Rev*. 2011; 30(3): 236–245.
17. Australian Institute of Health and Welfare. Drugs in Australia 2010: tobacco, alcohol and other drugs. Canberra: Australian Institute of Health and Welfare, 2011:73–83.
18. Sjogren P, Gronbaek M, Peuckmann V, Ekholm O. A population-based cohort study on chronic pain: the role of opioids. *Clin J Pain*. 2010; 26(9): 763–769.

19. Reid MC, Henderson CR Jr, Papaleontiou M, Amanfo L, Olkhovskaya Y, et al. Characteristics of older adults receiving opioids in primary care: treatment duration and outcomes. *Pain Med.* 2010; 11(7): 1063–1071.
20. Hariharan J, Lamb GC, Neuner JM. Long-term opioid contract use for chronic pain management in primary care practice. A five year experience. *J Gen Intern Med.* 2007; 22(4): 485–490.
21. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med.* 2010; 152(2): 85–92.
22. Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM, et al. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976).* 2008; 33(2): 199–204.
23. Pletcher MJ, Kertesz SG, Sidney S, Kiefe CI, Hulley SB. Incidence and antecedents of nonmedical prescription opioid use in four US communities. The Coronary Artery Risk Development in Young Adults (CARDIA) prospective cohort study. *Drug Alcohol Depend.* 2006; 85(2): 171–176.
24. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med.* 2002; 17(3): 173–179.
25. Hartung DM, Middleton L, Haxby DG, Koder M, Ketchum KL, et al. Rates of adverse events of long-acting opioids in a state Medicaid program. *Ann Pharmacother.* 2007; 41(6): 921–928.

26. Campbell G, Nielsen S, Bruno R, Lintzeris N, Cohen M, et al. The Pain and Opioids IN Treatment (POINT) study: characteristics of a cohort using opioids to manage chronic non-cancer pain. *Pain*. 2015; 156(2): 231-242.
27. Gadzhanova S, Bell JS, Roughead EE. What analgesics do older people use prior to initiating oxycodone for non-cancer pain? A retrospective database study. *Drugs Aging*. 2013; 30(11): 921–926.
28. Rogers KD, Kemp A, McLachlan AJ, Blyth F. Adverse selection? A multi-dimensional profile of people dispensed opioid analgesics for persistent non-cancer pain. *PLoS ONE*. 2013; 8(12): e80095.
29. Nielsen S, Degenhardt L, Hoban B, Gisev N. Comparing opioids: a guide to estimating oral morphine equivalents (OME) in research. NDARC Technical Report No. 329. Sydney: National Drug and Alcohol Research Centre, UNSW Australia, 2014.
30. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology. Oslo: Norwegian Institute of Public Health, 2008.
31. MIMS Australia: MIMS Online Drug Interactions. 2014.
32. Australian Medicines Handbook Pty Ltd. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd, 2014.
33. Baxter K, Preston CL eds. Stockley's Drug Interactions, 10th edn. London: Pharmaceutical Press, 2015.
34. Ringland C, Mant A, McGettigan P, Mitchell P, Kelman C, et al. Uncovering the potential risk of serotonin toxicity in Australian veterans using pharmaceutical claims data. *Br J Clin Pharmacol*. 2008; 66(5): 682–688.

35. Bachs LC, Bramness JG, Engeland A, Skurtveit S. Repeated dispensing of codeine is associated with high consumption of benzodiazepines. *Norsk Epidemiologi*. 2008; 18(2): 185–190.
36. Logan J, Liu Y, Paulozzi L, Zhang K, Jones C. Opioid prescribing in emergency departments: the prevalence of potentially inappropriate prescribing and misuse. *Med Care*. 2013; 51(8): 646–653.
37. White AG, Birnbaum HG, Schiller M, Tang J, Katz NP. Analytic models to identify patients at risk for prescription opioid abuse. *Am J Manag Care*. 2009; 15(12): 897–906.
38. Bramness JG, Furu K, Engeland A, Skurtveit S. Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol*. 2007; 64(2): 210–218.
39. Wilsey BL, Fishman SM, Gilson AM, Casamalhuapa C, Baxi H, et al. Profiling multiple provider prescribing of opioids, benzodiazepines, stimulants, and anorectics. *Drug Alcohol Depend*. 2010; 112(1-2): 99–106.
40. Han H, Kass PH, Wilsey BL, Li CS. Individual and county-level factors associated with use of multiple prescribers and multiple pharmacies to obtain opioid prescriptions in California. *PLoS ONE*. 2012; 7(9): e46246.
41. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Opioid shopping behavior: how often, how soon, which drugs and what payment method. *J Clin Pharmacol*. 2012; 53(1): 112–117.
42. Cepeda MS, Fife D, Yuan Y, Mastrogiovanni G. Distance traveled and frequency of interstate opioid dispensing in opioid shoppers and nonshoppers. *J Pain*. 2013; 14(10): 1158–1161.

43. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Assessing opioid shopping behaviour: a large cohort study from a medication dispensing database in the US. *Drug Saf.* 2012; 35(4): 325–334.
44. Peirce GL, Smith MJ, Abate MA, Halverson J. Doctor and pharmacy shopping for controlled substances. *Med Care.* 2012; 50(6): 494–500.
45. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, et al. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. *Pharmacoepidemiol Drug Saf.* 2004; 13(7): 473–481.
46. Braker LS, Reese AE, Card RO, van Howe RS. Screening for potential prescription opioid misuse in a Michigan Medicaid population. *Fam Med.* 2009; 41(10): 729–734.
47. Katz N, Panas L, Kim M, Audet AD, Bilanksy A, et al. Usefulness of prescription monitoring programs for surveillance—analysis of Schedule II opioid prescription data in Massachusetts, 1996–2006. *Pharmacoepidemiol Drug Saf.* 2010; 19(2): 115–123.
48. Rice JB, White AG, Birnbaum HG, Schiller M, Brown D, et al. A model to identify patients at risk for prescription opioid abuse, dependence, and misuse. *Pain Med.* 2012; 13(9): 1162–1173.
49. Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA.* 2012; 307(9): 940–947.
50. Holman CD. The impracticable nature of consent for research use of linked administrative health records. *Aust N Z J Public Health.* 2001; 25(5): 421–422.

51. Young AF, Dobson AJ, Byles JE. Health services research using linked records: who consents and what is the gain? *Aust N Z J Public Health*. 2001; 25(5): 417–420.
52. Secora AM, Dormitzer CM, Staffa JA, Dal Pan GJ. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiol Drug Saf*. 2014; 23(12): 1227–1237.
53. Blanch B, Mellish L, Buckley N, Dawson A, Haber PS, Pearson S. How is prescription opioid misuse measured, and what is the extent of opioid misuse globally? A systematic review of observational studies using routinely collected dispensing data (2000–2013). In: Global Addiction Conference. Rio de Janeiro, Brazil, 10–12 November, 2014.
54. Australian Bureau of Statistics. 1216.0.15.003—Australian Standard Geographical Classification (ASGC) Remoteness Area Correspondences, 2006. Canberra: Australian Bureau of Statistics, 2006.
55. Australian Bureau of Statistics. 1216.0—Australian Standard Geographical Classification (ASGC), July 2006. Canberra: Australian Bureau of Statistics, 2006.

### **Supplementary material:** POPPY project definition of opioid naïve

In relation to defining the cohort as “opioid naïve for at least 3-months prior to the index opioid prescription being supplied”, in this document we define opioid naïve, index prescription and write the logic for the drug dispensing history of a person INCLUDED in our data extraction.

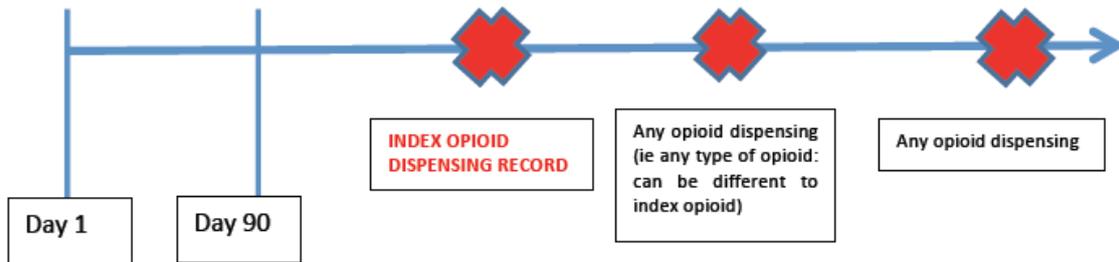
#### Definitions

- *Opioid naïve*: no opioid dispensing for  $\geq 90$  days.
- *Index prescription*: first opioid dispensing record after the opioid naïve period, i.e.  $\geq 90$  days.

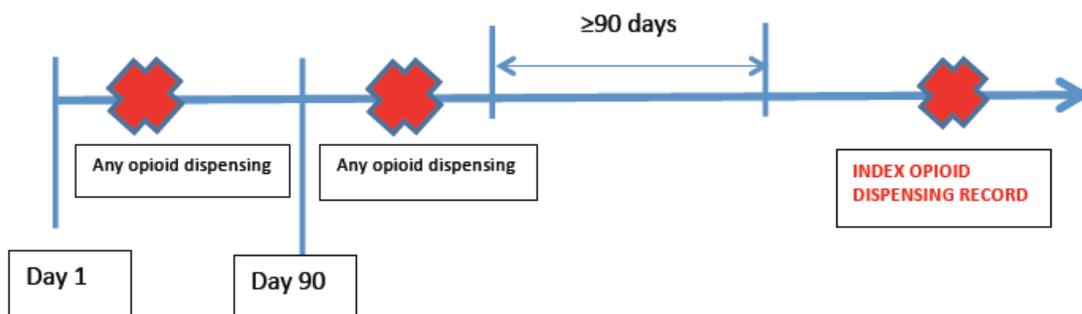
People who were eligible for inclusion in the cohort

We are interested in people with an opioid dispensing record (irrespective of the type of opioid dispensed; therefore searching was undertaken by ATC code rather than individual PBS item codes). All ATC codes related to any opioid were included. For people that have been dispensed  $\geq 1$  opioids during the data extraction period, there are two scenarios in which we want to **INCLUDE** people in the extraction: if a person’s opioid dispensing record is consistent with scenario **A or B** at any time throughout the data extraction period.

**Scenario A:** No opioid dispensing record in the first  $\geq 90$  days of available data; after this time period, the person has  $\geq 1$  opioid dispensing records (irrespective of the type of opioid dispensed).



**Scenario B:** A person was dispensed an opioid in the first 90 days of data available, BUT at some point during the data extraction period, there is a gap of  $\geq 90$  days between any two opioid dispensing records. The two opioid dispensing records can be for the same or different opioids.



For all people included in our cohort, we requested their complete drug dispensing history for the entire data extraction period. For example, if the data extraction period starts January 1, 2010; but the index opioid dispensing record occurs in December 2012, we want their dispensing records from January 1, 2010 to the final day of the data extraction period.

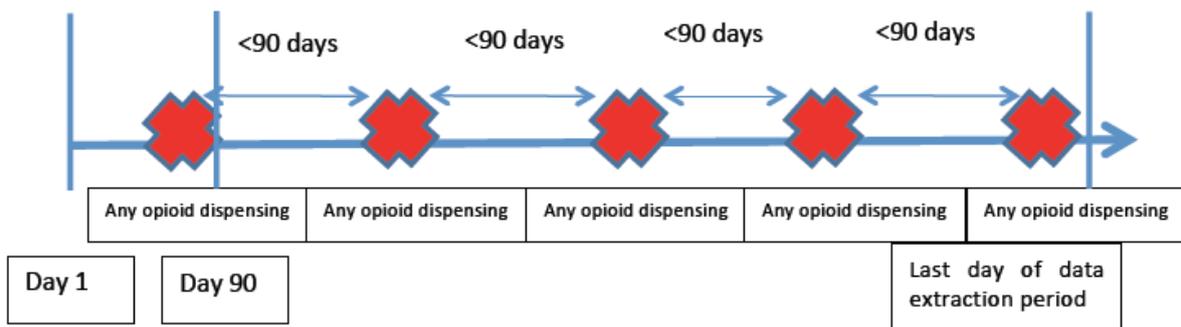
People who were not eligible for inclusion in the cohort

From this logic, we **EXCLUDED** scenarios **C through E**.

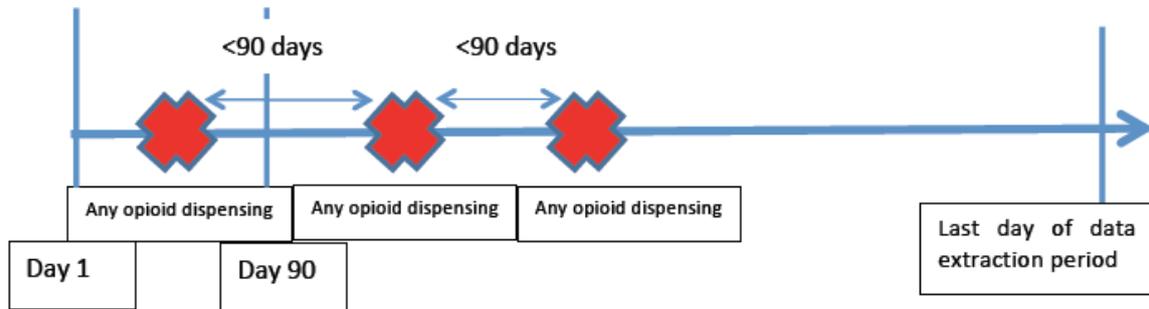
**Scenario C:** People without any opioid dispensing records in the entire data extraction period.



**Scenario D:** People with continuous use of opioids: persons with an opioid dispensing record in the first 90 days of data availability, and continuous opioid dispensing records throughout the data extraction period, i.e. <90 days gap between any two sequential opioid dispensing records.



**Scenario E:** Persons who stopped using opioids with no further opioid use: persons with an opioid dispensing record in the first 90 days of data availability, who have no further opioid dispensing records during the rest of the data extraction period.



***Chapter Six: Prescription opioid access patterns and factors associated with increasing number of prescribers, pharmacies and dispensings: an observational study using pharmaceutical claims***

In this chapter we build upon the findings of Chapter Four and further examine the associations between patient factors and increasing opioid access patterns across multiple metrics including number of prescribers, number of dispensing pharmacies and volume of drugs dispensed. To date, the literature has focused predominantly on the association between patient age and sex and potential misuse; relatively few studies have controlled for other factors including drug dispensing history.

This chapter is currently under consideration for publication; it has been peer-reviewed by *Pain Medicine*; we responded to reviewers' comments 20 October 2016.

Formatting note: To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. The abstract is formatted according to the *Pain Medicine* style guide. We provide the reference list at the end of this chapter. Supplementary materials are located after the reference list for this chapter.

## ***Abstract***

### *Objective*

To examine associations between patient factors and increasing opioid access measured by three metrics: number of unique prescribers, dispensing pharmacies and dispensings in 12 months.

### *Methods*

We used pharmaceutical claims for a random 10% sample of Australians aged  $\geq 18$  years initiating or reinitiating strong opioid treatment ( $\geq 90$ -days of no strong opioid dispensing) between July 2010 and December 2012. We report the distribution of opioid access by metric. We used three separate zero-truncated negative binomial regressions to explore associations. We censored individuals 365-days after index date or at death, whichever occurred first.

### *Results*

Approximately 69 088 persons initiated or reinitiated strong opioid treatment; they were predominantly female (59.7%) with a median age of 71 (interquartile range [IQR]: 58-81). Over one year, persons visited a median of two prescribers (IQR: 1-3), one dispensing pharmacy (IQR: 1-2) and had four opioid dispensings (IQR: 2-10). Three percent of people were in the top decile of opioid access distribution for all three metrics ( $\geq 4$  prescribers,  $\geq 3$  dispensing pharmacies or  $\geq 20$  dispensings). Increasing opioid access was strongly associated with male sex, history of pain treatment (3-12 months prior to index date) malignancy treatment or treatment for  $\geq 3$  other medical conditions.

### *Conclusions*

Delineating legitimate from extramedical opioid use based on pharmaceutical claims is imprecise. We demonstrated 'high' levels of access, defined in previous research, may reflect routine care for complex patients. Pharmaceutical claims have utility in examining population norms of prescription drug use and access patterns, and flagging persons at the extreme end of access, for at least one measure, who may warrant further investigation.

## **6.1 Introduction**

Over the past two decades, prescription opioid use has increased globally,<sup>1</sup> coinciding with expanding its indication to include the treatment of non-cancer as well as cancer pain. At this time, opioid-related harms including hospitalisations and deaths also increased.<sup>2-6</sup> In recognition of these escalating harms, the US Food and Drug Administration endorsed the post-market surveillance of opioids using routine data collections,<sup>7</sup> with a particular focus on identifying extramedical use<sup>8</sup> including doctor and pharmacy shopping.

Our recent systematic review, synthesised 13 years of international literature attempting to quantify extramedical use of prescription drugs in pharmaceutical claims. In the 52 studies reviewed, number of prescribers, number of dispensing pharmacies and volume of drugs dispensed were frequently used metrics defining extramedical use,<sup>9,10</sup> based on the assumption that higher access patterns are likely to be associated with harm to that individual or others. Despite these common metrics, we found 89 unique definitions of extramedical prescription drug use, 57 of which related to opioids. The vast majority of studies dichotomised access behaviours using a specific threshold delineating routine from extramedical use, which were predominantly based on previously published work, empirical analysis or expert opinion.<sup>9</sup> Few studies reported the full spectrum of access patterns (lowest to highest) or the determinants of higher access patterns.

The overall objective of this study was to explore the full spectrum of opioid access over a one-year period in Australian adults initiating or reinitiating strong opioid treatment between July 2010 and December 2012. We used national, population-based, person-level pharmaceutical claims to examine the distribution of opioid access in the year following the

date of initiating or reinitiating strong opioid treatment across three metrics: number of unique opioid prescribers, number of unique dispensing pharmacies for opioids and number of opioid dispensings. We also examined the association between patient characteristics and increasing opioid access patterns.

## **6.2 Methods**

### *6.2.1 Setting*

Australia has a publicly funded universal healthcare system entitling its 24 million citizens and permanent residents to a range of subsidised health services including free treatment in public hospitals, subsidised treatment in private hospitals and outpatient services, including subsidised prescription drugs via the Australian Pharmaceutical Benefits Scheme (PBS).<sup>11</sup>

### *6.2.2 Data source*

This study is part of the POPPY research project, evaluating the patterns and costs of prescription opioid use in Australia.<sup>12</sup> The data supplied by the Australian Government Department of Human Services (DHS) comprised the dispensing history of a 10% random sample of persons aged  $\geq 18$  years initiating or reinitiating strong opioid treatment<sup>13</sup> between 1 July 2009 and 31 December 2013, defined as a strong opioid dispensing after a period of at least 90-days where no strong opioids were supplied.

PBS data capture all dispensings (original and repeats) for PBS-subsidised prescription drugs that attract government subsidy, which occurs when the price of the drug is above the PBS copayment threshold.<sup>11</sup> As such, we have complete ascertainment of concessional beneficiaries' PBS records (persons receiving government benefits including the old age,

sickness, unemployment, single-parent or disability pension), as all PBS-subsidised drugs cost more than concessional beneficiaries' copayment amount (2009-2013: AU\$5.30-5.90).<sup>14</sup> Consequently, we restricted all analyses to concessional beneficiaries. Concessional beneficiaries comprise approximately 25% of the Australian population.<sup>15</sup>

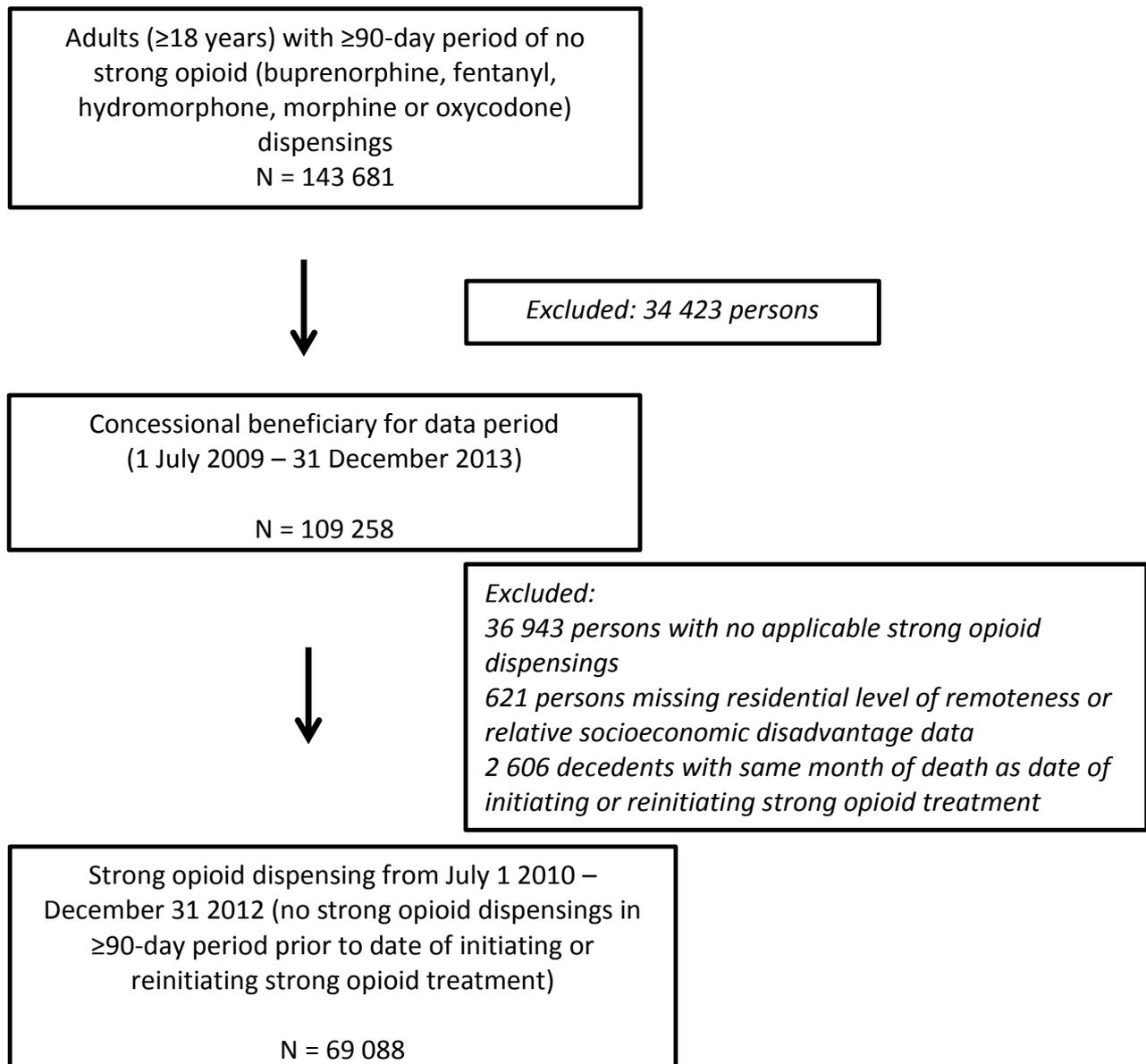
### *6.2.3 Prescription opioids of interest*

We use the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system code N02A to identify PBS-subsidised opioid analgesics dispensed for the indication of pain (Supplementary Table 6.1). We also use the WHO's cancer pain ladder for adults to categorise PBS-listed buprenorphine, fentanyl, hydromorphone, morphine or oxycodone as strong opioids and the mild opioids codeine and tramadol as weaker opioids.<sup>13</sup>

### *6.2.4 Study population (Figure 6.1)*

We restricted the study cohort to persons who were concessional beneficiaries for the entire data period (1 July 2009 to 31 December 2013 inclusive) and initiated or reinitiated strong opioid treatment between 1 July 2010 and 31 December 2012. By definition, our cohort does not include persons dispensed PBS-subsidised weaker opioids exclusively, or persons who do not have a gap of at least 90 days between strong opioid dispensings for all or part of the observation period.

**Figure 6.1** Cohort inclusion criteria



We observed cohort members for up to two years; 365 days prior to the date of initiating or reinitiating strong opioid treatment and 365 days from this date (inclusive). We censored persons 365 days after initiating or reinitiating strong opioid treatment or at death, whichever occurred first. If a person had multiple episodes of strong opioid treatment, we report only the first strong opioid treatment episode.

### *6.2.5 Study measures*

#### 6.2.5.1 Outcome measures

Number of unique opioid prescribers, number of unique dispensing pharmacies for opioids, and number of opioid dispensings recorded up to 365 days after the date of initiating or reinitiating strong opioid treatment (details in Table 6.1). To understand complete opioid access patterns, for each metric we counted all PBS-subsidised opioid dispensings (strong and weaker).

#### 6.2.5.2 Explanatory variables

On the date of initiating or reinitiating strong opioid treatment we recorded patient age (years), sex and location of patient residence (according to Statistical Local Area [SLA]). We used location of patient residence (SLA) as a proxy for residential level of remoteness and relative socioeconomic disadvantage of residence (see previous publications for further details).<sup>12,16,17</sup>

**Table 6.1** Summary and description of all measures and time period of assessment

Measure	Description <sup>a</sup>	Time period of assessment
<b>Outcome measures</b>		
Number of unique opioid prescribers	Total unique prescribers for any opioid dispensed <sup>b</sup>	365 days from date of initiating or reinitiating strong opioid treatment <sup>c,d</sup>
Number of unique opioid dispensing pharmacies	Total unique dispensing pharmacies for any opioid dispensed <sup>b</sup>	365 days from date of initiating or reinitiating strong opioid treatment <sup>c,d</sup>
Total opioid dispensings	Total number of opioid dispensings <sup>b</sup>	365 days from date of initiating or reinitiating strong opioid treatment <sup>c,d</sup>
<b>Explanatory variables</b>		
Age	Patient age (years) <i>Categories: 18-44; 45-64; 65-84; ≥85 years</i>	Date of initiating or reinitiating strong opioid treatment
Sex	Patient sex <i>Categories: female; male</i>	Date of initiating or reinitiating strong opioid treatment
Residential level of remoteness <sup>e</sup>	Proximity to services based on last known patient address based on 2011 Remoteness Area Indices <i>Categories: major city; inner regional; outer regional; remote/very remote</i>	Date of initiating or reinitiating strong opioid treatment
Relative socioeconomic disadvantage of residence <sup>e</sup>	Level of socioeconomic disadvantage based on last known patient address defined by Index of Relative Socioeconomic Disadvantage 2006 <i>Categories: lowest disadvantage; medium disadvantage; highest disadvantage</i>	Date of initiating or reinitiating strong opioid treatment
History of pain/inflammation (NSAID) treatment	Evidence of a prescription drug dispensing classified to treat condition of pain/inflammation according to the Rx-Risk tool (ATC code: M01AB01-M01AH06) <i>Categories: no; yes</i>	365 days prior to date of initiating or reinitiating strong opioid treatment <sup>f</sup>
History of pain (opioid) treatment	Evidence of a prescription drug dispensing classified to treat condition of pain according to the Rx-Risk tool (ATC	365 days prior to date of initiating or reinitiating strong opioid treatment <sup>f</sup>

	code: N02AA01-N02AX02) <i>Categories: no; yes</i>	
History of malignancy treatment	Evidence of a prescription drug dispensing classified to treat condition of malignancy according to the Rx-Risk tool (ATC code: L01AA01-L01XX31) <i>Categories: no; yes</i>	365 days prior to date of initiating or reinitiating strong opioid treatment <sup>f</sup>
Number of medical conditions <sup>g</sup>	Total unique medical conditions for which there is evidence of a prescription drug dispensing classified to treat one of 39 conditions according to the Rx-Risk tool (for all conditions and ATC codes see Supplementary Table 6.2). Maximum value is 39. <i>Categories: 0-2; 3-5; ≥6 conditions</i>	365 days prior to date of initiating or reinitiating strong opioid treatment <sup>f</sup>
<b>Exposure time</b>		
Days until death	Number of days from date of initiating or reinitiating strong opioid treatment to death. Our data includes month and year of death alone. To calculate time in model death dates were set to 16 <sup>th</sup> of the month.	365 days from date of initiating or reinitiating strong opioid treatment <sup>d</sup>

---

ATC: Anatomical Therapeutic Classification; NSAID: nonsteroidal anti-inflammatory drug

<sup>a</sup> Reference group is the first category listed

<sup>b</sup> Includes all PBS-subsidised opioids: buprenorphine, codeine (single and combination products), fentanyl, hydromorphone, methadone, morphine, oxycodone (single and combination products) and tramadol

<sup>c</sup> Or death, whichever occurred first

<sup>d</sup> Including date of initiating or reinitiating strong opioid treatment

<sup>e</sup> See references<sup>12,16,17</sup> for further details

<sup>f</sup> Excluding date of initiating or reinitiating strong opioid treatment

<sup>g</sup> Excluded conditions of pain/inflammation (NSAID), pain (opioid) and malignancy

In the year prior to initiating or reinitiating strong opioid treatment, we identified treatment for a number of medical conditions using the Rx-Risk tool (hereafter Rx-Risk), a validated measure using 12-month dispensing records to identify the treatment and presence of specific medical conditions<sup>18,19</sup> (Table 6.1, Supplementary Table 6.2). We identified separately the conditions of pain/inflammation (nonsteroidal anti-inflammatory drug [NSAID]), pain (opioid) and malignancy.

#### *6.2.6 Statistical analysis*

We characterised opioid access over one year for our three outcome measures using descriptive statistics (mean, range and medians with interquartile range). For each outcome, we detailed the number and proportion of persons exhibiting opioid access patterns equal to or above the 90<sup>th</sup> centile, and the overlap between metrics. We conducted further descriptive analyses, stratifying each metric by the number and proportion of persons, number and proportion of opioid dispensings, and patient factors of age; sex; history of pain/inflammation (NSAID), pain (opioid) and malignancy treatment, and number of medical conditions (excluding pain/inflammation [NSAID], pain [opioid] and malignancy).

Finally, we examined the association between each outcome measure and potential explanatory variables using three separate zero-truncated negative binomial multivariable regressions. This statistical analysis was required as each outcome was a count variable starting from one (cohort included persons with at least one opioid dispensing), meaning our outcome variables did not contain zeros. We used the negative binomial regression, an extension of the Poisson regression, that allows for overdispersion (where the variability of the data is larger than expected under the Poisson distribution).<sup>20</sup> Our explanatory variables

included patient age; sex; residential level of remoteness; relative socioeconomic disadvantage of residence; dispensing history of drugs for pain/inflammation (NSAID), pain (opioid) and malignancy treatment, and number of medical conditions (excluding pain/inflammation [NSAID], pain [opioid] and malignancy). In each regression model, we did not include either of the other two outcomes as explanatory variables in the models as all three outcomes were highly correlated and we were interested in the independent effects of patient factors on each specific opioid access pattern. For each multivariable model, we reported the incidence rate ratio (IRR) with 95% confidence intervals (CIs). We censored persons 365 days from initiating or reinitiating strong opioid treatment (inclusive) or at death; whichever occurred first. In our data, we received date of death as month and year of death, therefore, the precise temporal relationship between death and dispensing date are unknown. We therefore excluded persons who died in the same month as the date of initiating or reinitiating strong opioid treatment (n = 2 606) and conducted sensitivity analyses to assess the impact of this decision.

We used SAS software version 9.4 (SAS Institute, Cary, NC, USA) for all analyses.

#### *6.2.7 Ethics approval*

The Population and Health Services Research Ethics Committee approved this project (2013/10/481).

## **6.3 Results**

### *6.3.1 Cohort demographics (Table 6.2)*

We identified 69 088 concessional beneficiaries initiating or reinitiating strong opioid treatment between 1 July 2010 and 31 December 2012. The cohort was predominantly female (59.7%) with a median age of 71 (interquartile range [IQR]: 58-81) at cohort entry. Approximately 11% of the cohort was censored at death (median days from date of initiating or reinitiating strong opioid treatment to death: 108, IQR: 45-212).

In the year prior to initiating or reinitiating strong opioid treatment, two-thirds (67.7%) of the cohort were dispensed prescription drugs to treat  $\geq 3$  medical conditions and over one-quarter (29.3%) were treated for at least six medical conditions (excluding pain/inflammation [NSAID], pain [opioid] and malignancy). Only 4.4% were previously dispensed drugs to treat malignancy. Almost half (43.3%) were dispensed drugs for pain (opioid; includes both strong and weaker opioids) treatment in the 3 to 12 months prior to initiating or reinitiating strong opioid treatment. In the year prior to initiating or reinitiating strong opioid treatment, 60.2% of the cohort were dispensed an NSAID or paracetamol.

**Table 6.2** Cohort sociodemographics and clinical profile

	<b>Cohort N = 69 088</b>	<b>%</b>
<i>Sociodemographics<sup>a</sup></i>		
Female sex	41 241	59.7
Age group (years)		
18-44	9 735	14.1
45-64	13 113	19.0
65-84	34 930	50.6
≥85	11 310	16.4
Residential level of remoteness <sup>b</sup>		
Major city	43 494	63.0
Inner regional	17 846	25.8
Outer regional	7 045	10.2
Remote/very remote	703	1.0
Relative socioeconomic disadvantage of residence <sup>c</sup>		
Least disadvantage	21 076	30.5
Medium disadvantage	31 051	44.9
Highest disadvantage	16 961	24.6
<i>Clinical profile<sup>d</sup></i>		
History of pain/inflammation (NSAID) treatment	22 695	32.8
History of pain/inflammation (NSAID) or paracetamol <sup>e</sup> treatment	41 619	60.2
History of pain (opioid) treatment	29 884	43.3
History of malignancy treatment	3 057	4.4
Number of medical conditions <sup>f</sup>		
0-2	22 279	32.3
3-5	26 554	38.4
≥6	20 255	29.3

NSAID: nonsteroidal anti-inflammatory drug

<sup>a</sup> Measured at date of initiating or reinitiating strong opioid treatment

<sup>b</sup> Level of residential remoteness based on 2011 Remoteness Area Indices which considers distance for specific service centres

<sup>c</sup> Determined by Index of Relative Socio-economic Disadvantage (IRSD) 2006

<sup>d</sup> Evidence of a prescription drug dispensing classified to treat a specific medical condition as defined by the Rx-Risk tool in 12 months prior to date of initiating or reinitiating strong opioid treatment

<sup>e</sup> Paracetamol is not included in the Rx-Risk tool but is frequently prescribed for pain/inflammation. Paracetamol use identified based on ATC codes: N02BE01, N02BE51, N02BE71

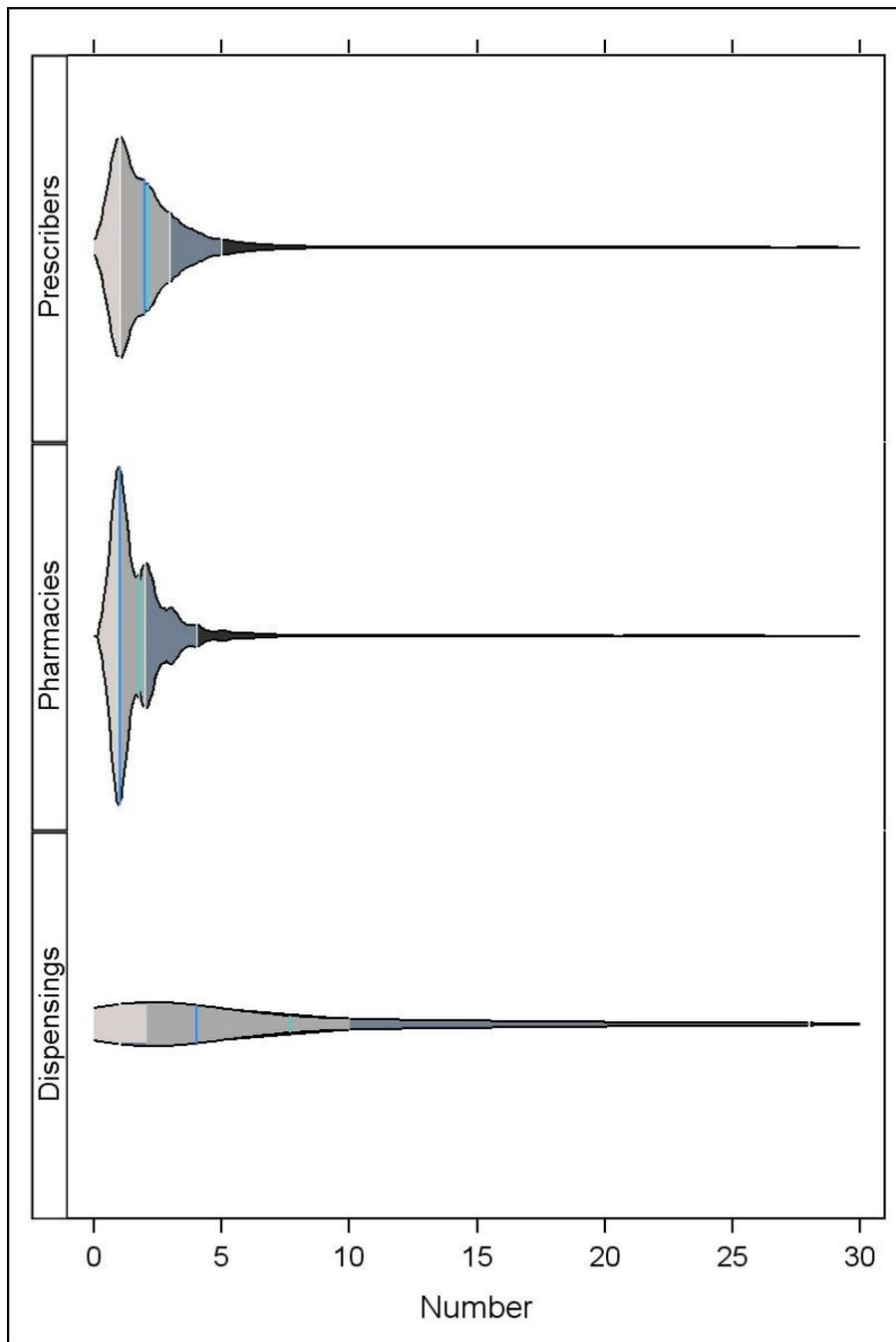
<sup>f</sup> Excluded medical conditions of pain, pain/inflammation and malignancy defined by Rx-Risk tool

### 6.3.2 Opioid use and access patterns

There were 530 215 opioid dispensing episodes for the cohort in the year after initiating or reinitiating strong opioid treatment. Oxycodone, buprenorphine and codeine together comprised more than 75% of opioid dispensings (42.1%, 20.2% and 14.9% respectively). To access all opioids (strong and weaker), persons visited a median of two unique prescribers (IQR: 1-3), one dispensing pharmacy (IQR: 1-2) and received four opioid dispensings (IQR: 2-10) (Figure 6.2). Over half the cohort (52.4%) visited  $\leq 2$  prescribers and one dispensing pharmacy to access opioids over one year; these persons obtained a median of two opioid dispensings (IQR: 1-4).

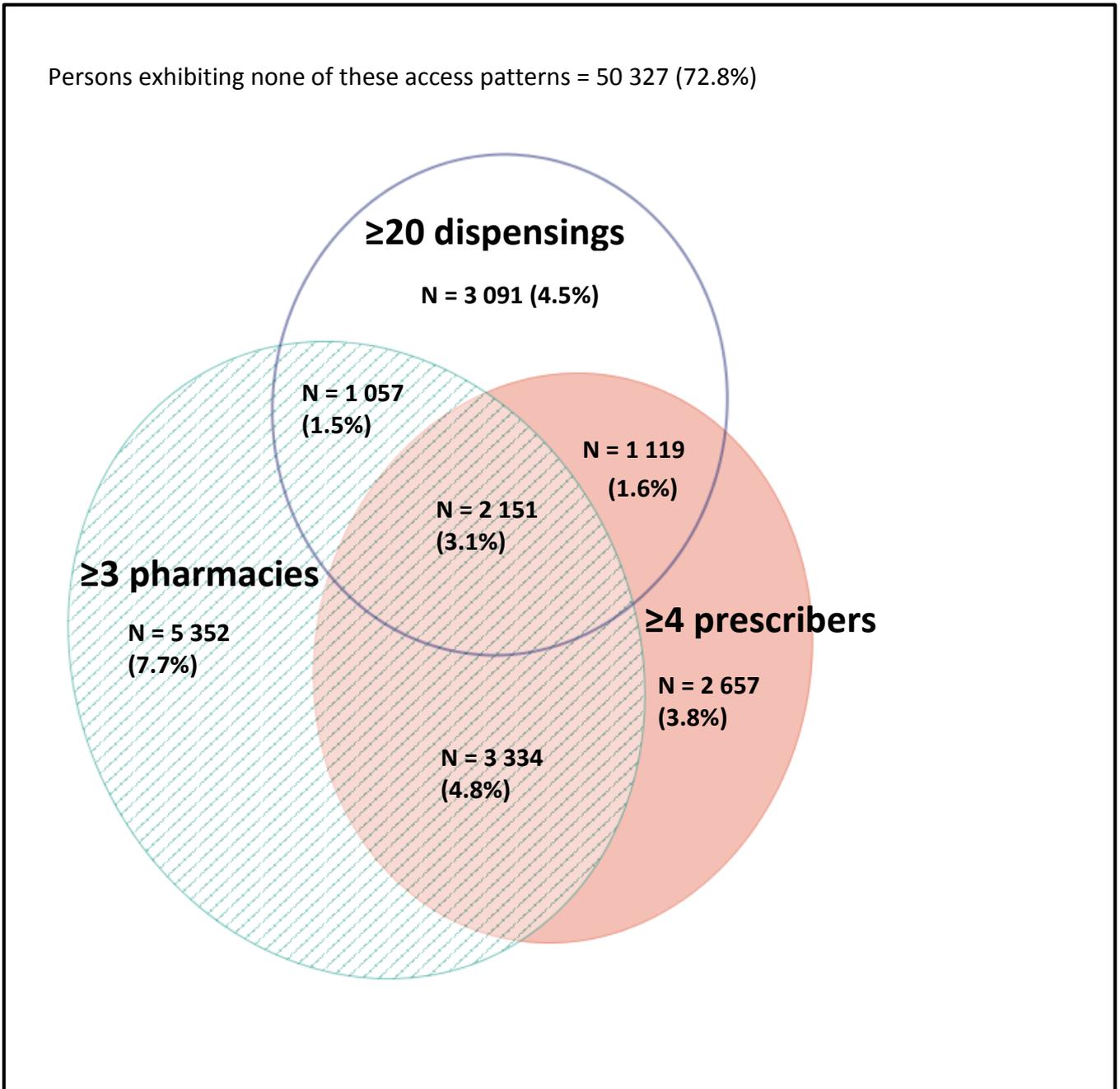
At the other end of the spectrum, the 90<sup>th</sup> centile for each metric was four prescribers, three dispensing pharmacies and 20 dispensings. In the cohort, 13.4% (n = 9 261) visited  $\geq 4$  prescribers, 17.2% (n = 11 894) visited  $\geq 3$  dispensing pharmacies and 10.7% (n = 7 418) obtained  $\geq 20$  dispensings; only 3.1% (n = 2 151) were in the top decile for all three metrics (Figure 6.3).

**Figure 6.2** Spectrum of opioid access patterns over one year after initiating or reinitiating strong opioid treatment: violin plot with shaded centile bounds



Legend: The X axis represents the number of opioid prescribers, dispensing pharmacies or dispensings accessed in 12 months. 1<sup>st</sup> to 25<sup>th</sup> centiles in brown; 26<sup>th</sup> to 75<sup>th</sup> centiles in grey; 76<sup>th</sup> to 94<sup>th</sup> centiles in darker grey; ≥95<sup>th</sup> centiles in black. Blue line indicates the median; turquoise line indicates the mean.

**Figure 6.3** Relationship between persons at the 90<sup>th</sup> centile or greater for at least one metric



*Factors associated with increasing opioid access patterns (Tables 6.3A-C and 6.4)*

We stratified access patterns for number of unique prescribers, dispensing pharmacies and dispensings by individual factors and opioid dispensings over one year (Tables 6.3A-C). As the value for each metric increased, the proportion of persons who exhibited the pattern decreased. For example, 47.4% of the cohort visited one prescriber whereas only 0.6% visited  $\geq 10$  prescribers. Generally, as the value for each metric increased, so did the proportion of persons with a history of treatment for pain/inflammation (NSAID) (one dispensing: 26.4% to 39.5% for  $\geq 31$  dispensings) or pain (opioid) (one prescriber: 34.1% to 75.3% for  $\geq 10$  prescribers).

The relationship with other patient factors varied by metric. As the number of prescribers or dispensing pharmacies increased, the median age and median number of medical conditions decreased. For example, the median age was higher for persons accessing one pharmacy (73; IQR: 61-82) compared to persons accessing  $\geq 10$  pharmacies (40; IQR: 34-49). Whereas for dispensings, as the number of dispensings increased both the median age and median number of conditions increased.

Finally, persons who visited at least three prescribers, at least two dispensing pharmacies or obtained at least eight dispensings, obtained disproportionately large amounts of opioids, i.e. the proportion of dispensed opioids obtained was larger than the proportion of persons exhibiting the access pattern (Tables 6.3A-C). This became particularly marked as the threshold increased; for example, 13.3% of persons visited  $\geq 4$  prescribers but obtained almost one-third (32.6%,  $n = 172\ 797$ ) of all opioid dispensings.

**Table 6.3A** Number of unique opioid prescribers stratified by dispensings, persons and individual factors

Cohort (N=69 088)			Individual factors <sup>a</sup>					
Unique opioid prescribers <sup>b,c</sup>	Opioid dispensings <sup>c</sup> (N, %)	Persons (N, %)	Age (years) <sup>d</sup> (Median, IQR)	Female sex <sup>d</sup> (N, %)	Pain/inflammation (NSAID) treatment <sup>e</sup> (N, %)	Pain (opioid) treatment <sup>e</sup> (N, %)	Malignancy treatment <sup>e</sup> (N, %)	Number of medical conditions <sup>e,f</sup> (Median, IQR)
1 prescriber	125 284 (23.6)	32 710 (47.4)	72 (60-82)	19 553 (59.8)	9 682 (29.6)	11 139 (34.1)	1 067 (3.3)	4 (2-6)
2 prescribers	134 879 (25.4)	18 238 (26.4)	72 (60-81)	10 930 (59.9)	6 263 (34.3)	8 410 (46.1)	784 (4.3)	4 (2-6)
3 prescribers	97 255 (18.3)	8 879 (12.9)	71 (60-81)	5 327 (60.0)	3 234 (36.4)	4 690 (52.8)	533 (6.0)	4 (2-6)
4 prescribers	63 780 (12.0)	4 373 (6.3)	71 (57-80)	2 643 (60.4)	1 682 (38.5)	2 549 (58.3)	292 (6.7)	4 (2-6)
5 prescribers	38 255 (7.2)	2 149 (3.1)	69 (53-79)	1 275 (59.3)	802 (37.3)	1 307 (60.8)	180 (8.4)	4 (2-6)
6 prescribers	23 666 (4.5)	1 124 (1.6)	69 (50-78)	645 (57.4)	421 (37.5)	691 (61.5)	79 (7.0)	4 (2-6)
7 prescribers	14 093 (2.7)	597 (0.9)	66 (47-78)	351 (58.8)	219 (36.7)	381 (63.8)	45 (7.5)	4 (2-6)
8 prescribers	8 766 (1.7)	347 (0.5)	63 (43-75)	175 (50.4)	125 (36.0)	226 (65.1)	26 (7.5)	4 (2-6)
9 prescribers	6 476 (1.2)	218 (0.3)	59 (39-74)	115 (52.8)	86 (39.5)	150 (68.8)	20 (9.2)	4 (1-6)
≥10 prescribers	17 761 (3.4)	453 (0.6)	49 (37-66)	227 (50.1)	181 (40.0)	341 (75.3)	31 (6.8)	3 (2-5)
<b>Entire cohort</b>	<b>530 215 (100)</b>	<b>69 088 (100)</b>	<b>71 (58-81)</b>	<b>42 179 (59.6)</b>	<b>22 695 (32.8)</b>	<b>29 884 (43.3)</b>	<b>3 057 (4.4)</b>	<b>4 (2-6)</b>

IQR: interquartile range; N: number; NSAID: nonsteroidal anti-inflammatory drug

<sup>a</sup> Denominator is 'persons' accessing same number of unique opioid prescribers

<sup>b</sup> Measured in 12 months after the date of initiating or reinitiating strong opioid treatment

<sup>c</sup> Any PBS-subsidised opioid: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone or tramadol

<sup>d</sup> Measured at the date of initiating or reinitiating strong opioid treatment

<sup>e</sup> Defined by Rx-Risk tool measured in 12 months prior to the date of initiating or reinitiating strong opioid treatment

<sup>f</sup> Excluded medical conditions of pain, pain/inflammation and malignancy as defined by Rx-Risk tool

**Table 6.3B** Number of unique opioid dispensing pharmacies stratified by dispensings, persons, and individual factors

Cohort (N=69 088)			Individual factors <sup>a</sup>					
Unique dispensing pharmacies for opioids <sup>b,c</sup>	Opioid dispensings <sup>c</sup> (N, %)	Persons (N, %)	Age (years) <sup>d</sup> (Median, IQR)	Female sex <sup>d</sup> (N, %)	Pain/inflammation (NSAID) treatment <sup>e</sup> (N, %)	Pain (opioid) treatment <sup>e</sup> (N, %)	Malignancy treatment <sup>e</sup> (N, %)	Number of medical conditions <sup>e,f</sup> (Median, IQR)
1 pharmacy	197 672 (37.3)	40 031 (57.9)	73 (61-82)	23 854 (59.6)	11 983 (29.9)	14 334 (35.8)	1 544 (3.9)	4 (2-6)
2 pharmacies	145 705 (27.5)	17 163 (24.8)	72 (59-81)	10 257 (59.8)	6 015 (35.1)	8 322 (48.5)	834 (4.9)	4 (2-6)
3 pharmacies	79 577 (15.0)	6 622 (9.6)	70 (55-79)	3 983 (60.2)	2 555 (38.6)	3 684 (55.6)	394 (6.0)	4 (2-6)
4 pharmacies	41 866 (7.9)	2 646 (3.8)	67 (50-77)	1 570 (59.3)	1 057 (40.0)	1 643 (62.1)	161 (6.1)	4 (2-6)
5 pharmacies	24 852 (4.7)	1 222 (1.8)	61 (44-73)	737 (60.3)	522 (42.7)	848 (69.4)	70 (5.7)	4 (2-6)
6 pharmacies	14 439 (2.7)	638 (0.9)	56 (40-71)	380 (59.6)	257 (40.3)	453 (71.0)	25 (3.9)	3 (2-5)
7 pharmacies	7 868 (1.5)	300 (0.4)	50 (38-67)	202 (67.3)	128 (42.7)	233 (77.7)	16 (5.3)	3 (2-5)
8 pharmacies	5 186 (1.0)	159 (0.2)	51 (39-66)	88 (55.4)	66 (41.5)	117 (73.6)	5 (3.1)	3 (2-5)
9 pharmacies	3 279 (0.6)	102 (0.2)	44 (35-57)	56 (54.9)	44 (43.1)	81 (79.4)	3 (2.9)	3 (2-5)
≥10 pharmacies	9 771 (1.9)	205 (0.3)	40 (34-49)	114 (55.6)	68 (33.2)	169 (82.4)	5 (2.4)	2 (1-4)
<b>Entire cohort</b>	<b>530 215 (100)</b>	<b>69 088 (100)</b>	<b>72 (59-81)</b>	<b>42 179 (59.6)</b>	<b>22 695 (32.8)</b>	<b>29 884 (43.3)</b>	<b>3 057 (4.4)</b>	<b>4 (2-6)</b>

IQR: interquartile range; N: number; NSAID: nonsteroidal anti-inflammatory drug

<sup>a</sup> Denominator is 'persons' accessing same number of unique dispensing pharmacies for opioids

<sup>b</sup> Measured in 12 months after the date of initiating or reinitiating strong opioid treatment

<sup>c</sup> Any PBS-subsidised opioid: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone or tramadol

<sup>d</sup> Measured at the date of initiating or reinitiating strong opioid treatment

<sup>e</sup> Defined by Rx-Risk tool measured in 12 months prior to the date of initiating or reinitiating strong opioid treatment

<sup>f</sup> Excluded medical conditions of pain, pain/inflammation and malignancy as defined by Rx-Risk tool

**Table 6.3C** Total opioid dispensings by dispensings, persons, and individual factors

Cohort (N=69 088)			Individual factors <sup>a</sup>					
Number of opioid dispensings <sup>b,c</sup>	Opioid dispensings <sup>c</sup> (N, %)	Persons (N, %)	Age (years) <sup>d</sup> (Median, IQR)	Female sex <sup>d</sup> (N, %)	Pain/inflammation (NSAID) treatment <sup>e</sup> (N, %)	Pain (opioid) treatment <sup>e</sup> (N, %)	Malignancy treatment <sup>e</sup> (N, %)	Number of medical conditions <sup>e,f</sup> (Median, IQR)
1 dispensing	17 087 (3.2)	17 087 (24.7)	70 (53-79)	10 023 (58.7)	4 513 (26.4)	4 148 (24.3)	543 (3.2)	3 (1-5)
2 dispensings	21 424 (4.0)	10 712 (15.5)	71 (55-80)	6 368 (59.5)	3 288 (30.7)	3 491 (32.6)	375 (3.5)	3 (1-6)
3 dispensings	20 034 (3.8)	6 678 (9.7)	71 (58-81)	3 912 (58.6)	2 210 (33.1)	2 692 (40.3)	303 (4.5)	4 (2-6)
4 dispensings	18 764 (3.5)	4 691 (6.8)	72 (59-81)	2 719 (58.0)	1 613 (34.4)	2 167 (46.2)	218 (4.7)	4 (2-6)
5 dispensings	17 465 (3.3)	3 493 (5.1)	72 (61-81)	2 087 (59.8)	1 220 (34.9)	1 653 (47.3)	155 (4.4)	4 (2-6)
6 dispensings	16 632 (3.1)	2 772 (4.0)	72 (61-82)	1 660 (59.9)	1 000 (36.1)	1 422 (51.3)	155 (5.6)	4 (2-6)
7 dispensings	15 848 (3.0)	2 264 (3.3)	72 (62-81)	1 346 (59.5)	853 (37.7)	1 177 (52.0)	138 (6.1)	4 (2-6)
8 dispensings	15 312 (2.9)	1 914 (2.8)	73 (62-82)	1 160 (60.6)	738 (38.6)	1 048 (54.8)	133 (7.0)	4 (2-6)
9 dispensings	14 463 (2.7)	1 607 (2.3)	73 (62-82)	955 (59.4)	590 (36.7)	929 (57.8)	82 (5.1)	4 (2-6)
10 dispensings	14 520 (2.7)	1 452 (2.1)	73 (63-82)	856 (59.0)	544 (37.5)	825 (56.8)	101 (7.0)	4 (3-6)
11-15 dispensings	74 832 (14.1)	5 971 (8.6)	74 (63-82)	3 534 (61.0)	2 168 (37.4)	3 521 (60.8)	324 (5.6)	5 (3-7)
16-20 dispensings	68 131 (12.8)	3 828 (5.5)	74 (63-83)	2 409 (62.9)	1 459 (38.1)	2 388 (62.4)	204 (5.3)	5 (3-7)
21-25 dispensings	55 226 (10.4)	2 417 (3.5)	75 (62-84)	1 512 (62.6)	886 (36.7)	1 540 (63.7)	131 (5.4)	5 (3-7)
26-30 dispensings	52 304 (9.9)	1 882 (2.7)	77 (64-86)	1 213 (64.5)	625 (33.2)	1 056 (56.1)	75 (4.0)	5 (3-7)
≥31 dispensings	108 173 (20.4)	2 500 (3.6)	69 (50-81)	1 487 (59.5)	988 (39.5)	1 827 (73.1)	120 (4.8)	4 (3-7)
<b>Entire cohort</b>	<b>530 215 (100)</b>	<b>69 088 (100)</b>	<b>72 (59-81)</b>	<b>42 179 (59.6)</b>	<b>22 695 (32.8)</b>	<b>29 884 (43.3)</b>	<b>3 057 (4.4)</b>	<b>4 (2-6)</b>

IQR: interquartile range; N: number; NSAID: nonsteroidal anti-inflammatory drug

<sup>a</sup> Denominator is 'persons' accessing same number of opioid dispensings

<sup>b</sup> Measured in 12 months after the date of initiating or reinitiating strong opioid treatment

<sup>c</sup> Any PBS-subsidised opioid: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone or tramadol

<sup>d</sup> Measured at the date of initiating or reinitiating strong opioid treatment

<sup>e</sup> Defined by Rx-Risk tool measured in 12 months prior to the date of initiating or reinitiating strong opioid treatment

<sup>f</sup> Excluded medical conditions of pain, pain/inflammation and malignancy as defined by Rx-Risk tool

**Table 6.4** Separate zero-truncated negative multivariable binomial regression models to examine factors associated with increasing number of unique opioid prescribers, dispensing pharmacies or dispensings in 12 months

	<b>Cohort (N=69 088)</b>	<b>Prescribers</b>	<b>Pharmacies</b>	<b>Dispensings</b>
	<b>N (%)</b>	<b>IRR (CI)</b>	<b>IRR (CI)</b>	<b>IRR (CI)</b>
<b>Age group (years)<sup>a</sup></b>				
18-44	9 735 (14.1)	Ref.	Ref.	Ref.
45-64	13 113 (19.0)	0.84 (0.81 to 0.88)	0.78 (0.75 to 0.81)	1.25 (1.20 to 1.31)
65-84	34 930 (50.6)	0.76 (0.73 to 0.78)	0.58 (0.55 to 0.60)	1.23 (1.19 to 1.30)
≥85	11 310 (16.4)	0.84 (0.80 to 0.89)	0.55 (0.52 to 0.58)	2.39 (2.27 to 2.53)
<b>Sex<sup>a</sup></b>				
Female	41 241 (59.7)	Ref.	Ref.	Ref.
Male	27 847 (40.3)	1.13 (1.11 to 1.16)	1.06 (1.04 to 1.09)	1.13 (1.09 to 1.15)
<b>Residential level of remoteness<sup>a</sup></b>				
Major city	43 494 (63.0)	Ref.	Ref.	Ref.
Inner regional	17 846 (25.8)	1.04 (1.01 to 1.07)	0.87 (0.84 to 0.90)	1.05 (1.01 to 1.08)
Outer regional	7 045 (10.2)	1.17 (1.13 to 1.22)	0.87 (0.84 to 0.91)	1.09 (1.05 to 1.15)
Remote/very remote	703 (1.0)	1.38 (1.23 to 1.55)	0.83 (0.73 to 0.93)	1.02 (0.89 to 1.17)
<b>Relative socioeconomic disadvantage of residence<sup>a</sup></b>				
Least disadvantage	21 076 (30.5)	Ref.	Ref.	Ref.
Medium disadvantage	31 051 (44.9)	1.04 (1.01 to 1.06)	0.99 (0.96 to 1.02)	1.01 (0.98 to 1.04)
Highest disadvantage	16 961 (24.6)	1.03 (1.00 to 1.07)	1.03 (0.99 to 1.07)	0.97 (0.93 to 1.01)
<b>History of pain/inflammation (NSAID) treatment<sup>b</sup></b>				
No	46 393 (67.2)	Ref.	Ref.	Ref.
Yes	22 695 (32.8)	1.03 (1.01 to 1.06)	1.11 (1.07 to 1.13)	1.00 (0.97 to 1.03)

History of pain (opioid) treatment <sup>b,c</sup>	39 204 (56.7)	Ref.	Ref.	Ref.
No	29 884 (43.3)	1.60 (1.57 to 1.65)	1.73 (1.68 to 1.79)	2.14 (2.08 to 2.20)
Yes				
History of malignancy treatment <sup>b</sup>				
No	66 031 (95.6)	Ref.	Ref.	Ref.
Yes	3 057 (4.4)	2.05 (1.93 to 2.18)	1.62 (1.52 to 1.72)	1.70 (1.58 to 1.82)
Number of medical conditions <sup>b,d</sup>				
0-2	22 279 (32.3)	Ref.	Ref.	Ref.
3-5	26 554 (38.4)	1.17 (1.14 to 1.21)	1.11 (1.07 to 1.15)	1.38 (1.34 to 1.43)
≥6	20 255 (29.3)	1.32 (1.28 to 1.38)	1.16 (1.12 to 1.20)	1.63 (1.58 to 1.70)

CI = 95% confidence interval; IRR = incidence rate ratio; NSAID = nonsteroidal anti-inflammatory drug; Ref. = reference category

<sup>a</sup> Measured at the date of initiating or reinitiating strong opioid treatment

<sup>b</sup> Defined by Rx-Risk tool measured in 12 months prior to date of initiating or reinitiating strong opioid treatment

<sup>c</sup> Strong opioids dispensed prior to ≥90-day period of no strong opioid dispensings

<sup>d</sup> Excluded medical conditions of pain/inflammation (NSAID), pain (opioid) and malignancy as defined by the Rx-Risk tool

Our descriptive results were largely consistent with the multivariable regression analyses (Table 6.4). We found males were 6-13% more likely to exhibit increasing opioid access patterns compared to females. Older persons ( $\geq 45$  years) accessed fewer prescribers and pharmacies than younger persons (18-44 years), but obtained more opioid dispensings. Persons living in regional or remote areas visited more prescribers, but fewer pharmacies than persons living in a major city. There was limited evidence that relative socioeconomic disadvantage of residence was associated with any outcome after adjusting for other factors.

Across all outcomes, the strongest factors associated with increasing opioid access patterns were a history of pain (opioid) or malignancy treatment. We found limited associations between a history of pain/inflammation (NSAID) treatment and increasing opioid access patterns after adjusting for other factors. For all three outcomes, persons with increasing number of medical conditions had higher access patterns than their counterparts with fewer medical conditions. Of note, our descriptive analysis demonstrated a decrease in median number of medical conditions as number of prescribers or dispensing pharmacies increased; controlling for age in the multivariable regression analyses reversed the direction of this association.

In all analyses we excluded persons who died in the same month as initiating or reinitiating strong opioid treatment ( $n = 2\ 606$ ). We conducted a sensitivity analysis to explore the impact of this decision by replicating our three zero-truncated negative binomial multivariable regression analyses and including these persons. The results for these sensitivity analyses were almost identical to our original results for number of prescribers

and dispensing pharmacies (Supplementary Table 6.3). However, the incidence risk ratio (IRR) of obtaining multiple opioid dispensings increased considerably for persons aged  $\geq 85$  years and persons with a history of malignancy treatment.

#### **6.4 Discussion**

In this cohort, the majority of people initiating or reinitiating strong opioid treatment exhibited unremarkable access patterns. Specifically, over two-thirds of the cohort visited one or two prescribers or dispensing pharmacies over one year to access their prescription opioids. These people obtained two-fifths of all dispensed opioids and had a median of two opioid dispensings over one year.

In our systematic review quantifying extramedical use of prescription drugs in pharmaceutical claims, only six of the 52 reviewed studies reported the distribution of prescription drug access for at least one metric.<sup>9</sup> To date, only three studies, all from the US, have reported the spectrum of opioid access patterns over one year using pharmaceutical claims.<sup>21-23</sup> These studies reported 83-92% of persons visited one or two opioid prescribers over one year<sup>21,22</sup> and 52-98% visited up to two pharmacies.<sup>22,23</sup> The difference in proportions reflects the cohort definition; studies with a more restrictive inclusion criteria, such as 3 months of continuous opioid use prior to index date, generally report lower proportions of persons visiting 1-2 prescribers/dispensing pharmacies.

There is considerable variation in the extent of extramedical opioid use reported across studies. In our systematic review we found the extent of extramedical opioid use ranged from <1% to 63.2%, with similar figures (<1% to 81%) reported in a recent review examining

extramedical opioid use in adults with chronic pain.<sup>10,24</sup> In our review, estimates were dependent on the use of single or combined metrics and thresholds delineating routine use from extramedical use. Generally, when extramedical use is defined using higher thresholds and/or multiple metrics, the reported level of misuse is lower. In the current study, over one-quarter of the cohort exhibited access patterns in the top decile for at least one metric ( $\geq 4$  prescribers,  $\geq 3$  pharmacies or  $\geq 20$  dispensings). Based on our review of previous literature, any one of these access patterns would have been considered extramedical use.<sup>9</sup>

In our study, 3% of persons exhibited access patterns in the top decile for all three metrics. Compared to the entire cohort, these persons were younger (52% aged 18-64 years) and obtained a disproportionately large amount of opioid dispensings (14%). These characteristics were consistent with previous literature profiling 'misusers'.<sup>25</sup> Compared to the entire cohort, persons who exhibited access patterns in the top decile for all three metrics, also had a higher proportion of persons with a history of malignancy treatment (7% versus 4%) and a higher median number of medical conditions (6 versus 3). Our findings were consistent with a recent US Medicare study; as the number of prescribers increased so did the proportion of persons dispensed antineoplastic, stimulant, central nervous system, neuromuscular and non-opioid analgesic drugs.<sup>21</sup> These findings suggest sicker persons have increasing opioid access, which may be consistent with routine medical care, rather than extramedical use. However, disease severity is difficult to determine based on pharmaceutical claims alone; only the treating physician would have all the information necessary to assess whether the volume of drugs procured from visiting multiple doctors and pharmacies were for legitimate medical or extramedical purposes.

Our study had several limitations. As with previous studies included in our systematic review, we have focused on access patterns and therefore the potential risk of harm that could be attributed to higher patterns of use. These studies which rely solely on dispensing claims do not have the capacity to identify harms with normal use, for example excessive sedation occurring with initiation. Moreover our cohort was restricted to initiators and reinitiators of strong opioid treatment, and thus excluded most long-term strong opioid use. We restricted our cohort to concessional beneficiaries (persons receiving a government pension) as we have their complete PBS dispensing history. Our data did not capture any under-copayment dispensings or private prescriptions which together accounted for 18% of opioid use in 2011.<sup>26</sup> Further, our data did not capture dispensings for non-PBS-listed prescription opioids including dextropropoxyphene and tapentadol nor over-the-counter (OTC) codeine (only OTC opioid available in Australia), which accounted for at least 56% of all prescription and OTC codeine sales in 2013.<sup>27, 28</sup> Therefore, our results underestimate total opioid use and access patterns. Moreover, our previous research demonstrated the length of the look-back period impacts on the formation of cohorts in new-user study designs.<sup>29</sup> However, we previously demonstrated the POPPY cohort demographics were similar whether we adopted a 3, 6 or 12-month opioid-free period.<sup>16</sup>

## **6.5 Conclusions**

Despite the recent push to quantify extramedical opioid use via routinely collected health data, this study demonstrated the challenges in delineating routine from extramedical use based on pharmaceutical claims alone. Pharmaceutical claims have utility in examining population norms of prescription drug use and access patterns, and flagging persons at the extreme end of access, for at least one measure, who may warrant further investigation.

## 6.6 References

1. Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet*. 2016; 387: 1644–1656.
2. Blanch B, Pearson SA, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. *Br J Clin Pharmacol*. 2014; 78: 1159–1166.
3. Dhalla IA, Mamdani MM, Sivilotti MLA, Kopp A, Qureshi O, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ*. 2009; 181: 891–896.
4. Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, et al. Opioid epidemic in the United States. *Pain Physician*. 2012; 15: ES9–38.
5. Fischer B, Jones W, Urbanoski K, Skinner R, Rehm J. Correlations between prescription opioid analgesic dispensing levels and related mortality and morbidity in Ontario, Canada, 2005–2011. *Drug Alcohol Rev*. 2014; 33: 19–26.
6. Centers for Disease Control Prevention. CDC grand rounds: prescription drug overdoses – a US epidemic. *MMWR Morb Mortal Wkly Rep*. 2012; 61: 10.
7. Kux L. Postmarketing requirements for the class-wide extended-release/long-acting opioid analgesics; public meeting; request for comments. *Fed Regist*. 2014; 79: 22499–22501.
8. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick R. Definitions related to the use of pharmaceutical opioids: extramedical use, diversion, non-adherence and aberrant medication-related behaviours. *Drug Alcohol Rev*. 2011; 30: 236–45.

9. Blanch B, Buckley NA, Mellish L, Dawson AH, Haber PS, et al. Harmonizing post-market surveillance of prescription drug misuse: a systematic review of observational studies using routinely collected data (2000–2013). *Drug Saf.* 2015; 38 : 553–564.
10. Blanch B, Mellish L, Buckley N, Dawson A, Haber P, et al. How is prescription opioid misuse measured, and what is the extent of opioid misuse globally? A systematic review of observational studies using routinely collected dispensing data (2000–2013). *Journal of Addictive Behaviors, Therapy & Rehabilitation.* 2014; in press.
11. Mellish L, Karanges E, Litchfield M, Schaffer A, Blanch B, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMC Res Notes.* 2015; 8: 634.
12. Degenhardt L, Blanch B, Gisev N, Larance B, Pearson S. The POPPY Research Programme protocol: investigating opioid utilisation, costs and patterns of extramedical use in Australia. *BMJ Open.* 2015; 5: e007030.
13. World Health Organization. WHO's cancer pain ladder for adults 2016 [Available from: <http://www.who.int/cancer/palliative/painladder/en/>. Accessed 20 January 2016.
14. Pharmaceutical Benefits Scheme. Fees, patient contributions and safety net thresholds 2015. Available from: <http://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee>. Accessed 29 June 2016.
15. Department of Health and Ageing. Trends in and drivers of Pharmaceutical Benefits Scheme expenditure 2013 [Available from: <http://www.pbs.gov.au/statistics/asm/2010/australian-statistics-on-medicine-2010.pdf>. Accessed 29 June 2016.
16. Gisev N, Pearson S, Blanch B, Larance B, Dobbins T, et al. Initiation of strong prescription opioid analgesics in Australia: cohort characteristics and factors

- associated with the type of opioid analgesic initiated. *Br J Clin Pharm*. 2016; 82: 1123–1133.
17. Australian Bureau of Statistics. Australian Standard Geographical Classification (ASGC) 2011 [Available from: [http://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/32FBEDE1EA4C5800CA25791F000F2E1C/\\$File/att98dqt.pdf](http://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/32FBEDE1EA4C5800CA25791F000F2E1C/$File/att98dqt.pdf)]. Accessed 17 October 2016.
  18. Sloan KL, Sales AE, Liu C-F, Fishman P, Nichol P, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care*. 2003; 41: 761–74.
  19. Lu CY, Barratt J, Vitry A, Roughead E. Charlson and Rx-Risk comorbidity indices were predictive of mortality in the Australian health care setting. *J Clin Epidemiol*. 2011; 64: 223–228.
  20. Coxe S, West SG, Aiken LS. The analysis of count data: a gentle introduction to Poisson regression and its alternatives. *J Pers Assess*. 2009; 91: 121-136.
  21. Jena AB, Goldman D, Weaver L, Karaca-Mandic P. Opioid prescribing by multiple providers in Medicare: retrospective observational study of insurance claims. *BMJ*. 2014; 348: 1393.
  22. Katz N, Panas L, Kim M, Audet AD, Bilansky A, et al. Usefulness of prescription monitoring programs for surveillance – analysis of Schedule II opioid prescription data in Massachusetts, 1996–2006. *Pharmacoepidemiol Drug Saf*. 2010; 19: 115–123.
  23. Yang Z, Wilsey B, Bohm M, Weyrich M, Roy K, et al. Defining risk of prescription opioid overdose: pharmacy shopping and overlapping prescriptions among long-term opioid users in Medicaid. *J Pain*. 2015; 16: 445–453.

24. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015; 156: 569–576.
25. Pauly V, Frauger E, Pradel V, Rouby F, Berbis J, et al. Which indicators can public health authorities use to monitor prescription drug abuse and evaluate the impact of regulatory measures? Controlling high dosage buprenorphine abuse. *Drug Alcohol Depend*. 2011; 113: 29–36.
26. Karanges EA, Blanch B, Buckley NA, Pearson SA. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. *Br J Clin Pharm*. 2016; 82: 255–267.
27. Degenhardt L, Gisev N, Cama E, Nielsen S, Larance B, et al. The extent and correlates of community-based pharmaceutical opioid utilisation in Australia. *Pharmacoepidemiol Drug Saf*. 2016; 25: 521–538.
28. Gisev N, Nielsen S, Cama E, Larance B, Bruno R, et al. An ecological study of the extent and factors associated with the use of prescription and over-the-counter codeine in Australia. *Eur J Clin Pharmacol*. 2016; 72: 469–494.
29. Blanch B, Daniels B, Litchfield M, Pearson SA. Looking forward and looking back: the balancing act in new drug user designs for pharmacoepidemiological research. *Pharmacoepidemiol Drug Saf*. 2015; 24: 1117–1119.

**Supplementary Table 6.1** List of all PBS-subsidised opioid analgesics and Anatomical Therapeutic

Chemical code

<b>ATC code</b>	<b>Generic drug name</b>	<b>Opioid type<sup>a</sup></b>
N02AE01	Buprenorphine	Strong
R05DA04 <sup>b</sup> (N02AA59, N02AA79)	Codeine (combinations)	Weaker
N02AB03	Fentanyl	Strong
N02AA03	Hydromorphone	Strong
N02AC	Methadone	Strong
N02AA01	Morphine	Strong
N02AA05 (N02AA55)	Oxycodone (combinations)	Strong
N02AX02	Tramadol	Weaker

ATC: Anatomical Therapeutic Chemical

<sup>a</sup> Opioid classification based on World Health Organization cancer pain ladder for adults<sup>13</sup>

<sup>b</sup> Codeine dispensed under this ATC code may be dispensed for the indication of cough suppression or pain

**Supplementary Table 6.2** List of Rx-Risk tool defined medical conditions and Anatomical

Therapeutic Chemical codes

<b>Medical condition (defined by Rx-Risk tool)</b>	<b>ATC codes</b>
Alcohol dependence	N07BB03-N07BB04; V03AA01
Allergies	R01AC01-R01AD60; R06AD02-R06AX26
Anticoagulation	B01AA03-B01AB06
Antiplatelet	B01AC04-B01AC30
Anxiety	N05BA01-N05BA12
Arrhythmia	C01AA05, C01BA01-C01BD01
Benign prostate hyperplasia	G04CA02-G04CA03, G04CB01
Bipolar	N06AX
Congestive heart failure	C03CA01-C03CC01
Dementia	N06DA02-N06DA04
Depression	N06AA01-N06AG02, N06AX03-N06AX18
Diabetes	A10AA01-A10BG03
End stage renal disease	B03XA01-B03XA02; A11CC01-A11CC04; V03AE02
Epilepsy	N03AA01-N03AX14
Gastric acid disorder	A02BA01-A02BX05
Glaucoma	S01EA01-S01EB03; S01EC03-S01EX
Gout	M04AA01-M04AC01
Hepatitis C	J05AB54
HIV	J05AE-J05AE08; J05AF01-J05AG03; J05AR; J05AX07
Hyperkalaemia	V03AE01
Hyperlipidaemia	C10AA01-C10BX03
Hypertension	C03AA01-C03BA11; C03DA01-C03AE01; C09BA02-C09BA09; C09DA02-C09DA07; C02AB01-C02AC05; C02DB02-C02KX01
Hypothyroidism	H03AA01-H03AA02
IHD angina	C01DA02-C01DA14
IHD hypertension	C07AA01-C07AB03; C07AG01-C08DB01
Inflammatory bowel disease	A07EC01-A07EC04; A07EA01-A07EA02
Liver failure	A06AD11
Malignancy	L01AA01-L01XX31
Malnutrition	B05BA03
Migraine	N02CA01-N02CX01
Osteoporosis/Paget's disease	M05BA01-M05BB03
Pain	N02AA01-N02AX02
Pain/inflammation	M01AB01-M01AH06
Pancreatic insufficiency	A09AA02
Parkinson's disease	N04AA01-N04BX02
Psoriasis	D05AA; D05BB01-D05BB02; D05AX02
Psychotic illness	N5AA01-N05AB02; N05AB06-N05AX12
Reactive airway disease	R03AC02-R03DC03
Smoking cessation	N07BA01-N07BA02
Steroid responsive disease	H02AB01-H02AB10

Transplant  
Tuberculosis

L04AA01-L04AA21  
J04AB04-J04AK02

---

ATC: Anatomical Therapeutic Chemical

**Supplementary Table 6.3** Sensitivity analysis results: separate zero-truncated negative binomial regression models to examine factors associated with increasing number of unique opioid prescribers, dispensing pharmacies or dispensings in 12 months

	<b>Cohort (N=71 685)</b>	<b>Prescribers</b>	<b>Pharmacies</b>	<b>Dispensings</b>
	<b>N (%)</b>	<b>IRR (CI)</b>	<b>IRR (CI)</b>	<b>IRR (CI)</b>
<b>Age group (years)<sup>a</sup></b>				
18-44	9 750 (13.6)	Ref.	Ref.	Ref.
45-64	13 197 (18.4)	0.84 (0.81 to 0.88)	0.78 (0.75 to 0.81)	1.26 (1.20 to 1.34)
65-84	35 855 (50.0)	0.76 (0.73 to 0.79)	0.58 (0.56 to 0.61)	1.34 (1.27 to 1.40)
≥85	12 883 (18.0)	0.89 (0.84 to 0.93)	0.55 (0.53 to 0.58)	3.86 (3.60 to 4.10)
<b>Sex<sup>a</sup></b>				
Female	42 657 (59.5)	Ref.	Ref.	Ref.
Male	29 028 (40.5)	1.15 (1.12 to 1.17)	1.07 (1.05 to 1.11)	1.21 (1.17 to 1.26)
<b>Residential level of remoteness<sup>a</sup></b>				
Major city	43 494 (63.1)	Ref.	Ref.	Ref.
Inner regional	18 482 (25.8)	1.04 (1.01 to 1.07)	0.88 (0.84 to 0.90)	1.04 (1.00 to 1.08)
Outer regional	7 257 (10.1)	1.17 (1.12 to 1.22)	0.87 (0.84 to 0.91)	1.07 (1.02 to 1.14)
Remote/very remote	728 (1.0)	1.36 (1.22 to 1.54)	0.82 (0.72 to 0.93)	0.98 (0.84 to 1.14)
<b>Relative socioeconomic disadvantage of residence<sup>a</sup></b>				
Least disadvantage	21 735 (30.3)	Ref.	Ref.	Ref.
Medium disadvantage	32 193 (44.9)	1.03 (1.01 to 1.06)	0.99 (0.96 to 1.02)	1.01 (0.97 to 1.05)
Highest disadvantage	17 757 (24.8)	1.04 (1.00 to 1.07)	1.03 (1.00 to 1.07)	0.98 (0.94 to 1.03)
<b>History of pain/inflammation (NSAID) treatment<sup>b</sup></b>				
No	48 727 (68.0)	Ref.	Ref.	Ref.
Yes	22 958 (32.0)	1.02 (0.99 to 1.05)	1.09 (1.06 to 1.13)	0.93 (0.90 to 0.96)

History of pain (opioid) treatment <sup>b,c</sup>				
No	41 196 (57.5)	Ref.	Ref.	Ref.
Yes	30 489 (42.5)	1.60 (1.55 to 1.63)	1.73 (1.68 to 1.77)	2.14 (2.05 to 2.20)
History of malignancy treatment <sup>b</sup>				
No	68 445 (95.5)	Ref.	Ref.	Ref.
Yes	3 240 (4.5)	2.14 (2.01 to 2.27)	1.67 (1.55 to 1.77)	2.03 (1.88 to 2.20)
Number of medical conditions <sup>b,d</sup>				
0-2	22 648 (31.6)	Ref.	Ref.	Ref.
3-5	27 598 (38.5)	1.17 (1.14 to 1.21)	1.12 (1.08 to 1.15)	1.46 (1.40 to 1.52)
≥6	21 439 (29.9)	1.34 (1.30 to 1.39)	1.16 (1.13 to 1.21)	1.86 (1.77 to 1.93)

CI: 95% confidence interval; IRR: incidence rate ratio; NSAID: nonsteroidal anti-inflammatory drug; Ref.: reference category

<sup>a</sup> Measured at date of initiating or reinitiating strong opioid treatment

<sup>b</sup> Defined by Rx-Risk tool measured in 12 months prior to date of initiating or reinitiating strong opioid treatment

<sup>c</sup> Strong opioids dispensed prior to ≥90-day period of no strong opioid dispensings

<sup>d</sup> Excluded medical conditions of pain/inflammation (NSAID), pain (opioid) and malignancy as defined by the Rx-Risk tool

***Chapter Seven: Looking forward and looking back: the balancing act  
in new drug user designs for pharmacoepidemiological research***

In Chapter Six we examined the associations between patient factors and increasing opioid access patterns in persons initiating or reinitiating strong opioid treatment. We defined an initiation/reinitiation as  $\geq 90$  days of no strong opioid dispensings prior to a strong opioid dispensing. We used this definition as we previously demonstrated there was little difference in the opioid cohort composition based on a longer opioid-free period of 180 or 365 days.

However, for future pharmacoepidemiology studies it is important to understand the impact of the length of the look-back period on results and cohort composition. In this chapter, we examine this question for three drug classes: antipsychotics, opioids including codeine preparations and opioids excluding codeine preparations.

This chapter is based on the following publication:

Bianca Blanch, Benjamin Daniels, Melisa Litchfield, Sallie-Anne Pearson. Looking forward and looking back: the balancing act in new drug user designs for pharmacoepidemiological research. *Pharmacoepidemiology and Drug Safety*. 2015; 24: 157-158.

Formatting note: To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. The key points and

abstract are formatted according to the *Pharmacoepidemiology and Drug Safety* style guide.

We provide the reference list at the end of this chapter.

### ***Key Points***

- There is no 'one-size-fits-all' approach to new-user study designs.
- Length of the look-back period will depend on the prescription drug and outcome of interest.

To the Editor,

It has long been known that the length of a look-back period to determine new versus previous users of a specific drug can introduce misclassification and bias study findings. In a large cohort of Danish children dispensed asthma drugs and antibiotics, Riis et al. recently showed that new user designs using look-back periods of 2 years can introduce severe misclassification.<sup>1</sup>

We are currently undertaking a program of research in Australia examining the use and outcomes associated with prescription antipsychotic and opioid analgesics. We have been developing our study methodology based on different look-back periods. To add further evidence to the Riis et al. study, we detail our experience in quantifying the effect of 10 look-back periods on the misclassification of new users of antipsychotics and opioid analgesics (with and without codeine preparations) in Australian adults.

Australia has a publically funded universal healthcare system entitling all citizens and permanent residents to a range of subsidised health services including prescription drugs via the Pharmaceutical Benefits Scheme (PBS).

The Australian Government Department of Human Services (DHS) established a standardised dataset of PBS dispensing claims for a random 10% sample of Australians in March 2005 (MI2593 and MI2779). We have a contract with DHS for use of these data for pharmacoepidemiological research with quarterly data updates. A record is created in this dataset when an individual receives government subsidy for a PBS-listed drug. An individual

is eligible for subsidy when the drug is priced above the patient copayment amount.

Australia has a two-tiered copayment system meaning that low-cost PBS-listed drugs dispensed to individuals with the highest copayment (general beneficiaries) are not captured in this dataset. However, all prescription drugs are priced above the concessional beneficiary copayment meaning we have complete ascertainment of all PBS-listed drugs dispensings for this patient group. We focus our analyses on the latter group.

The drug classes of interest include antipsychotics (ATC code: N05A) and opioid analgesics (ATC codes: N02A, R05DA04, N07BC [methadone for the indication of pain alone]).

Our study population included persons aged  $\geq 18$  years at 1 January 2005 and concessional beneficiaries for the entire period between 1 July 2005 and 30 June 2014. For each drug class of interest, we categorised persons as true new users (dispensing between 1 July 2012 and 30 June 2014 and no dispensings between 1 July 2005 and 30 June 2012) or true prior users (dispensing between 1 July 2012 and 30 June 2014 and a dispensing between 1 July 2005 and 30 June 2012). This project was approved by the Population and Health Services Research Ethics Committee (2013/11/494).

We calculated the relative misclassification (RM) based on 10 look-back periods: 1, 3 and 6 months and annual look-back periods from 1 to 7 years, defined as the time period prior to each individual's index dispensing. We calculated the RM of new users by dividing the number of defined new users (dispensing between 1 July 2012 and 30 June 2014 and no dispensings during the look-back period of interest) by the number of true new users. We

calculated RM and 95% confidence intervals (using bootstrap methods) for each look-back period.

We identified 24 375 antipsychotic users between 1 July 2012 to 30 June 2014. RM decreased from 2.51 at 1 month to 1.01 at 7 years. We identified 132 153 opioid users including codeine preparations and 80 333 opioid users excluding codeine preparations. RM decreased from 3.61 at 1 month to 1.08 at 7 years and 2.23 at 1 month to 1.04 at 7 years, respectively (Table 7.1).

Consistent with the findings of Riis et al, our study shows that varying look-back periods impact on the RM of new users<sup>1</sup> and that RM is higher for drugs used intermittently (opioids are likely to be used intermittently). Opioid users excluding codeine preparations had a median of three dispensings (interquartile range [IQR]: 1-14) in two years compared with 10 antipsychotic dispensings (IQR: 3-23). The RM for opioids in our analysis was higher than antipsychotics across all look-back periods longer than 1 month. Within opioids, we have demonstrated that including codeine preparations increases the RM.

We have recently undertaken a systematic review of all Australian studies using PBS data for pharmacoepidemiological research.<sup>2</sup> Seven studies investigating antipsychotics or opioid analgesics employed a new user design, and all used a look-back period of 12 months. Based on our findings, the potential RM for the antipsychotic or opioid studies were 1.31 or 2.72, respectively.

**Table 7.1** Relative misclassification for new adult antipsychotic and opioid analgesic users for each look-back period of interest

	<b>Antipsychotics N = 24 375</b>			<b>Opioid analgesics (including codeine) N = 132 153</b>			<b>Opioid analgesics (excluding codeine) N = 80 333</b>		
Female (N, %)	13 207	54.2		79 591	60.2		49 525	61.7	
Age at 1 July 2012 (median, IQR)	61	44-80		68	50-78		72	57-80	
Dispensings (median, IQR) <sup>a</sup>	10	3-23		2	1-9		3	1-14	
True new users (N, %)	7 774	31.9		32 529	24.6		30 831	38.4	
Prior users (N, %)	16 601	68.1		99 624	75.4		49 502	61.6	
<b>Look-back period<sup>b</sup></b>	<b>New users (N)</b>	<b>RM</b>	<b>(95% CI)</b>	<b>New users (N)</b>	<b>RM</b>	<b>(95% CI)</b>	<b>New users (N)</b>	<b>RM</b>	<b>(95% CI)</b>
0 days	24 375	3.14	-	132 153	4.06	-	80 333	2.61	-
1 month	19 481	2.51	(2.48-2.53)	117 459	3.61	(3.60-3.62)	68 599	2.23	(2.22-2.23)
3 months	12 973	1.67	(1.64-1.70)	106 217	3.27	(3.26-3.27)	62 042	2.01	(2.01-2.02)
6 months	11 147	1.43	(1.41-1.46)	99 364	3.05	(3.05-3.06)	59 210	1.92	(1.91-1.93)
12 months	10 194	1.31	(1.29-1.33)	88 537	2.72	(2.71-2.73)	54 958	1.78	(1.77-1.79)
2 years	9 281	1.19	(1.17-1.22)	70 800	2.18	(2.17-2.19)	47 738	1.55	(1.54-1.56)
3 years	8 735	1.12	(1.10-1.14)	57 765	1.78	(1.77-1.79)	42 151	1.37	(1.36-1.38)
4 years	8 423	1.08	(1.06-1.10)	49 390	1.52	(1.51-1.53)	38 472	1.25	(1.24-1.26)
5 years	8 174	1.05	(1.03-1.07)	43 327	1.33	(1.32-1.34)	35 802	1.16	(1.15-1.17)
6 years	8 013	1.03	(1.01-1.05)	38 783	1.19	(1.18-1.20)	33 723	1.09	(1.09-1.10)
7 years	7 883	1.01	(0.99-1.03)	35 229	1.08	(1.07-1.09)	32 129	1.04	(1.03-1.05)

RM: relative misclassification; 95% CI: 95% confidence interval

<sup>a</sup> Dispensings between 1 July 2012 and 30 June 2014

<sup>b</sup> Look-back period: time period prior to each individual's index dispensing during the observation period

However, our study demonstrates that there is no 'one-size-fits-all' approach to new user study designs, and the length of the look-back period will depend on the prescription drug and outcome of interest. Like Riis et al., we encourage researchers to undertake sensitivity analyses to determine the influence of the look-back period on study outcomes. Clearly, new user pharmacoepidemiological research studies should use lengthy look-back periods. Ideally, dispensing claims linked with other routinely collected health data should be available from birth to minimise RM. Yet in reality, researchers in most jurisdictions do not have the luxury of the whole-of-population, linked data available in Scandinavian countries. Therefore, pragmatic considerations play into decisions about look-back periods. It is a balancing act – the longer the look-back period, the shorter the look-forward period. We encourage more studies, like Riis et al., to shed light on this important but under-researched aspect of potential misclassification bias in pharmacoepidemiological research.

## **7.1 References**

1. Riis AH, Johansen MB, Jacobsen JB, Brookhart MA, Sturmer T, et al. Short look-back periods in pharmacoepidemiologic studies of new users of antibiotics and asthma medications introduce severe misclassification. *Pharmacoepidemiol Drug Saf.* 2015; 24(5): 478-485.
2. Pearson S, Pesa N, Langton J, Drew A, Faedo M, et al. Studies using Australia's Pharmaceutical Benefits Scheme data for pharmacoepidemiological research: a systematic review of the published literature (1987-2013). *Pharmacoepidemiol Drug Saf.* 2015; 24(5): 447-455.

## ***Chapter Eight: Discussion***

The work outlined in this thesis provides the foundation to better understand the capacity of pharmaceutical claims to identify and quantify prescription drug ‘misuse’. In this concluding chapter we discuss the implications of our study findings and the potential of our research to inform evidence-based strategies to reduce prescription drug misuse and related harms in the future.

To increase the readability of viewing this thesis electronically, we provide all figures or tables on the page following its first citation in the text. We provide the reference list at the end of this chapter.

## **8.1 Key findings and future research directions**

### *8.1.1 Limitations of the traditional threshold approach to quantify prescription drug misuse*

Our research demonstrates the possibilities and challenges of quantifying prescription drug misuse in pharmaceutical claims. One of the challenges of using pharmaceutical claims alone to quantify misuse is the nature of these data; they contain limited clinical information and a finite set of variables. To date, the global literature has predominantly utilised specific thresholds based on access patterns to delineate appropriate use from potential misuse. However, these thresholds are largely based on expert consensus or previous literature and most have not been validated.

In our research we used alternative methodologies to the threshold approach. We examined the full spectrum of prescription drug access patterns and benchmarked access across drug classes with known and no known abuse potential, to establish how an approach of this kind may better inform the primary aims of our work. We demonstrated access patterns for individual drug classes were remarkably similar across two jurisdictions with universal healthcare arrangements. However, there were marked differences in access patterns in the higher centiles between prescription drug classes with high and no known abuse potential. These differences may identify access patterns associated with individual or societal harm.

Furthermore, we examined the factors associated with increasing opioid access patterns across three metrics used commonly to define misuse. This approach

clearly demonstrated the limitations of the threshold methodology in quantifying prescription drug misuse based on pharmaceutical claims, as it is likely to identify persons with high levels of comorbid and/or chronic disease who may be accessing and taking opioids appropriately, as well as a group of people who are likely to be misusing these drugs. At best, the traditional threshold method could be used as a marker of a potential problem; this approach does not have the capacity to accurately quantify misuse.

#### *8.1.2 Pharmaceutical claims in quantifying misuse: limitations and future potential*

Given pharmaceutical claims are collected for the purpose of administering prescription drug subsidy programs it is highly unlikely they will ever contain all the information necessary to inform this important research, clinical and policy agenda. Information currently missing from pharmaceutical claims includes the medical indication for use, and, specifically in Australian data, prescribed daily dose and treatment duration. Moreover, until recently PBS claims did not contain all PBS-listed drugs dispensed in Australia, only those where the dispensing attracted a Commonwealth subsidy.

The potential of routinely collected data to inform efforts to quantify and ultimately curb prescription drug misuse are likely to be realised when pharmaceutical data are linked to other routinely collected health outcome data to establish the association between prescription drug access patterns and harm.

Australia is in a unique position to lead this global effort due to its universal healthcare system, large stores of routinely collected health data and capacity for linkage across disparate data collections. However, until recently data linkage efforts have been hampered due to legislative barriers, privacy concerns and the fragmented nature of health data collections.<sup>1</sup> Specifically, hospital data (including hospital admissions and emergency department [ED] presentations) and registries (cancer notifications and death) are under the custodianship of individual Australian States and Territories, whereas community health service data and PBS dispensing claims are under the custodianship of the Commonwealth.

Despite the establishment of Commonwealth-approved data integrating authorities, such as the Australian Institute of Health and Welfare,<sup>2</sup> to link population-level cross-jurisdictional data, linkages are very costly, resource intensive and time consuming. Moreover, national prescription drug use and outcomes studies would require approval across nine jurisdictions, from at least 10 human research ethics committees (HRECs) and more than 30 data custodians. Not surprisingly, Australia's research output in pharmacoepidemiological studies is modest relative to other jurisdictions with universal healthcare systems such as the Scandinavian countries.<sup>1</sup> Due to this challenging data linkage environment, researchers currently face the trade-off between accessing cross-jurisdictional data, that is likely to take a minimum of two years to obtain all relevant HREC approvals and these data may cost in excess of AU\$100 000 dollars; or, access whole-of-population data through the lens of one healthcare payer, as is the case with this thesis.

## ***8.2 Examining drug access patterns and harm***

A potential compromise, or first step, to explore drug use and outcomes in Australia is to establish a cross-jurisdictional linkage based on residents living in New South Wales (NSW) and the Australian Capital Territory (ACT). NSW is the most populous Australian state (7.5 million people), and the ACT (400,000 people) is bordered entirely by NSW. Due to the geographic location of the ACT there is likely cross-border health service utilisation by Australian residents living close to the State border.<sup>3</sup> A population of almost 8 million people would yield sufficient power to examine specific prescription drug exposures and rare outcomes. Importantly, this approach would substantially reduce the administrative burden in accessing these data; for example a linkage of this kind would require approval from only three HRECs. Below we detail the necessary data infrastructure, using prescription opioids as the case example, to deliver this program.

### ***8.2.1 Data linkage and datasets***

To investigate the associations between prescription drug use, access patterns and harm one would establish a cohort of prescription opioid exposed persons ascertained through PBS claims. These claims could be linked to the following State-based datasets: prescription opioid dispensings to treat opiate dependence (Section 100 – Highly Specialised Drugs Program), hospital separations, ED presentations, and mortality data (fact and cause of death). There may also be merit in linking State-based cancer notification data to identify persons who are likely to be treated for cancer rather than non-cancer pain. These State collections could be linked to Medicare Benefits Schedule (MBS) data. We provide a data summary in Table 8.1.

**Table 8.1.** Summary of other routinely collected health datasets available to link to Pharmaceutical Benefits Scheme dispensing data

Data	Summary of captured data	Use
<i>State-based data collection</i>		
Section 100 – Highly Specialised Drugs Program (S100 HSDP)	State-collected data that records dispensing information for drugs prescribed for the treatment of chronic conditions which, because of their clinical use or other special features, are restricted to supply through public or private hospitals having access to appropriate specialist facilities. <sup>4</sup> Opioids, such as methadone and buprenorphine, dispensed for the indication of opiate dependence are classified as highly specialised drugs.	Drug exposure and outcome/harm
Hospital separations	State-collected data that records all hospital separations and services/procedures provided to admitted patient in public hospitals, public psychiatric hospitals, public multi-purpose services, private hospitals and private day procedure centres. <sup>5</sup>	Outcome/harm
Emergency department presentations	State-collected data that records information for emergency department presentations in public hospitals. <sup>5</sup>	Outcome/harm
Mortality data	State-collected data that provides information regarding death from the Registry of Births, Deaths and Marriages, and the Australian Bureau of Statistics Cause of Death Unit Record File. <sup>5</sup>	Outcome/harm
Cancer notification data	State-collected data that details health information for a persons index cancer diagnosis. <sup>5</sup>	Outcome/harm
<i>National data collection</i>		
Medicare Benefits Scheme (MBS) data	Nationally-collected dataset that captures Medicare services subsidised by the Australian Government. <sup>6</sup> The <i>Health Insurance Act 1973</i> stipulates that Medicare benefits are payable for a professional service, define as a clinically relevant service listed on the MBS such as pathology tests and psychological consultations. <sup>6</sup>	Drug exposure and outcome/harm

Importantly, linking any of these datasets with PBS claims would provide the opportunity to examine the nuances of prescription opioid use and harms, validate measures of 'misuse' developed through pharmaceutical claims and examine trajectories likely to lead to misuse or other harms. To date, only one Australian study has linked a cohort of young adults who experienced a heroin overdose death with their MBS and PBS claims. They found as year of death approached the cohort had considerably higher healthcare interactions.<sup>7</sup> However, this study focused on illicit opioids, no Australian studies has undertaken a cross-jurisdictional linkage to examine prescription opioid use and outcomes in the general population. Consequently, there are no published studies using person-level linked data examining individual patterns of prescription opioid use and outcomes.

Internationally, multiple studies have linked pharmaceutical claims with outcomes data,<sup>7-24</sup> the majority of which examined associations between patient and clinical factors, and negative outcomes including overdose, diagnosis of opioid misuse or death.<sup>7-24</sup> Patient factors associated with negative outcomes include male sex; younger age;<sup>18,21,23,24</sup> and, previous diagnoses such as substance abuse or depression;<sup>9,11,22,24</sup> Clinical factors associated with these outcomes include increasing opioid dose;<sup>8,9,11,12,14-16,20,21,24</sup> dispensing of specific opioids or formulations, such as buprenorphine or long-acting opioids respectively;<sup>11,13,19,21,22</sup> dispensing of other classes of prescription drugs such as benzodiazepines;<sup>12,17,20,21,23</sup> and, opioid access patterns.<sup>8,17,21,22,24</sup> Consistent with our findings throughout this thesis, these studies found a minority of patients accessed multiple prescribers or pharmacies, but as the number of prescribers, pharmacies or dispensings increased so did the risk of a negative outcome.

The limitations of these studies mirror those we identified in our systematic review detailed in Chapter Two. Opioid cohort definitions were heterogeneous across studies, ranging from one opioid dispensing to  $\geq 3$  months of continuous opioid use. We demonstrated throughout this thesis that cohort definitions impact cohort size, demographics and/or opioid access patterns, which limits the opportunity for comparisons across studies. The definition of the outcomes of interest also varied across studies, which may also impact on study findings. No studies examined whole-of-population, national data. The majority of studies were set in the US (13 studies; 72%)<sup>8-12,14,15,17,19-22,24</sup>; 10 studies (56%) included a particular patient population such as veterans; Medicare/ Medicaid enrollees or privately insured persons,<sup>9-11,14,15,17,19,20,22,24</sup> of these, six studies used national data.<sup>9,10,17,19,20,22</sup> As previously highlighted in this thesis, relying on death certificates to identify persons with an opioid-related death will likely result in under ascertainment of cases as the cause of death may be recorded as due to another related cause such as respiratory depression, particularly in older persons. Despite these limitations, these studies demonstrate the evidence-base in this field is increasing regarding prescription opioid use and outcomes and we are beginning to identify high-risk patient groups, as well as assess the effectiveness of strategies and health policies to reduce prescription drug misuse.

The evidence-base in this field would be strengthened if studies from different jurisdictions examine prescription drug access patterns. By adopting a similar methodology, we can conduct comparisons between jurisdictions to examine common prescription drug access patterns. Where there are differences in access patterns across jurisdictions, we have the opportunity to investigate factors that facilitate and/or act as a barrier to prescription drug access/misuse, which may include healthcare arrangements, prescribing patterns and health

policy. For example, few Scandinavian studies have examined prescription opioid misuse or 'shopping' behaviours as they are rare occurrences.<sup>25,26</sup> Consequently, there may be limited perceived public health benefit to examine prescription drug access patterns in these jurisdictions.

However, from a global public health perspective, curbing prescription drug misuse is a priority so understanding why there is a lack of opioid misuse in these jurisdictions warrants further investigation. In Australia, we have a universal healthcare provider and a data linkage project provides the opportunity to link national pharmaceutical claims, via the PBS, with outcomes data for at least one State/Territory. To understand and define prescription drug misuse, we must first understand the norms of prescription drug access.

### ***8.3 Gaps in Pharmaceutical Benefits Scheme data***

As detailed previously, PBS data were established for the primary purpose of administering payments for PBS-listed prescription drug dispensings. Consequently, the variables contained within these collections are those required to administer the program. In this section, we outline the PBS data gaps that, if filled, would strengthen these data and enhance routine monitoring and research efforts.

Traditionally, only dispensed drugs attracting a government subsidy form part of the PBS dataset, which is managed by the Australian Government Department of Human Services (DHS). However, in 2012, the Pharmacy Guild Survey agreement was renegotiated whereby PBS-listed drugs that did not attract a government subsidy (e.g. under-copayment drugs) were also provided to DHS in unit record form.<sup>27</sup> This addition led to more complete pharmaceutical data collection, for example, between 2014-2015 over one-quarter of all

drug dispensings in Australia were for under-copayment drugs.<sup>28</sup> While mechanisms to access under-copayment data are under development, routine access for approved research studies will be available in the near future.

The Public Hospital Pharmaceutical Reforms allow participating hospitals to provide discharging inpatients and outpatients with PBS-subsidised drugs.<sup>29</sup> These Reforms were introduced in Victoria (2001), Queensland (2002), Western Australia (2002), Northern Territory (2007), South Australia (2008) and Tasmania (2010). As no agreement currently exists between the NSW or ACT public hospitals, these States in-hospital drug dispensings are not included in the PBS collection.

Private dispensings occur when a prescription drug is either: not PBS-listed, or PBS-listed but prescribed for an indication that is not PBS-approved. In 2011, almost 7% of all opioids were dispensed via a private prescription but the proportion of private dispensings varied by drug.<sup>30</sup> It is reasonable to assume the proportion of dispensings obtained via private prescription will vary across drug class and over time. As detailed previously, due to the Pharmacy Guild Survey ceasing in 2012, there is no unit-record data collection of private prescriptions.

We also recommend other information available to dispensing pharmacists should be captured in these data. The prescribed daily dose (PDD) is the amount of drug prescribed per day to the patient to treat the relevant medical condition. Despite this information being detailed on prescriptions and collected by pharmacists to print on the packaging of the dispensed drug, this information is not recorded in PBS claims. Furthermore, the

quantity field in PBS data refers to the total amount of the drug dispensed to the patient rather than the amount recommended for treatment. For example, 5 mg tablets of oxycodone are currently dispensed in a pack size of 20 tablets; a patient may require four tablets per day therefore one pack would be dispensed whether the treatment was for two or five days. Due to the absence of these two data points, Australian researchers are required to create proxies for important exposures and/or outcomes of interest such as duration of treatment, discontinuation of therapy and delineating switching behaviour from concomitant therapy.

While these enhancements would address some important data gaps, even with these additions, the PBS dataset alone is not sufficient to fully understand access patterns that place people at most risk of harm.

#### ***8.4 Implications for policy and practice***

In 2014, the US Food and Drug Administration (FDA) committed publically to curbing the abuse and misuse of prescription opioids while still retaining access for persons requiring these drugs to manage pain. As part of the declaration, they endorsed the use of routinely collected data to define and quantify prescription opioid misuse.<sup>31</sup> Initiatives such as prescription drug monitoring programs (PDMPs) have been developed in response to the escalating use and harm associated with prescription drugs, particularly opioids. PDMPs allow a prescriber or pharmacist to examine an individual's dispensing history to determine whether they have obtained excessive, and potentially harmful, amounts of prescription drugs. Of note, three of the 18 studies (17%) linking pharmaceutical claims with outcomes data used PDMP data.<sup>8,12,21</sup> PDMP data may prove to be a vital resource in examining

associations between prescription drug dispensings and outcomes, particularly in the US, as these data capture all prescription drug dispensings for controlled drugs, regardless of the patient's age or health insurance status.

PDMPs have been implemented in almost every US State.<sup>32</sup> The effectiveness of PDMPs in reducing prescription rates for controlled substances, misuse or harms are unclear due to the nuances of each system.<sup>43-48</sup> In an effort to harmonise PDMP data collections across the US, the Drug Enforcement Agency created a list of the ideal features of a PDMP (Table 8.2).<sup>49</sup> An essential feature of every PDMP should be its capacity to implement a red flag, to identify persons exhibiting access patterns associated with harms. To achieve this goal, a close collaboration between researchers and policy makers is required.

**Table 8.2.** US Drug Enforcement Agency list of features in an ideal prescription drug monitoring program<sup>49</sup>

<b>Features of an ideal prescription drug monitoring program</b>
Ease of access
Standardised content
Real-time updates
Mandatory pharmacy reporting
Monitoring of concerning prescription drugs (Schedules 2-5) <sup>a</sup>
Interstate accessibility
Confidentiality and security
Support for public health initiatives
Capability for strictly monitored access by non-prescribers

<sup>a</sup> Schedules 2-5 in the US equates to at least Schedules 4 (prescription only drugs) and 8 (controlled drugs) in Australia.

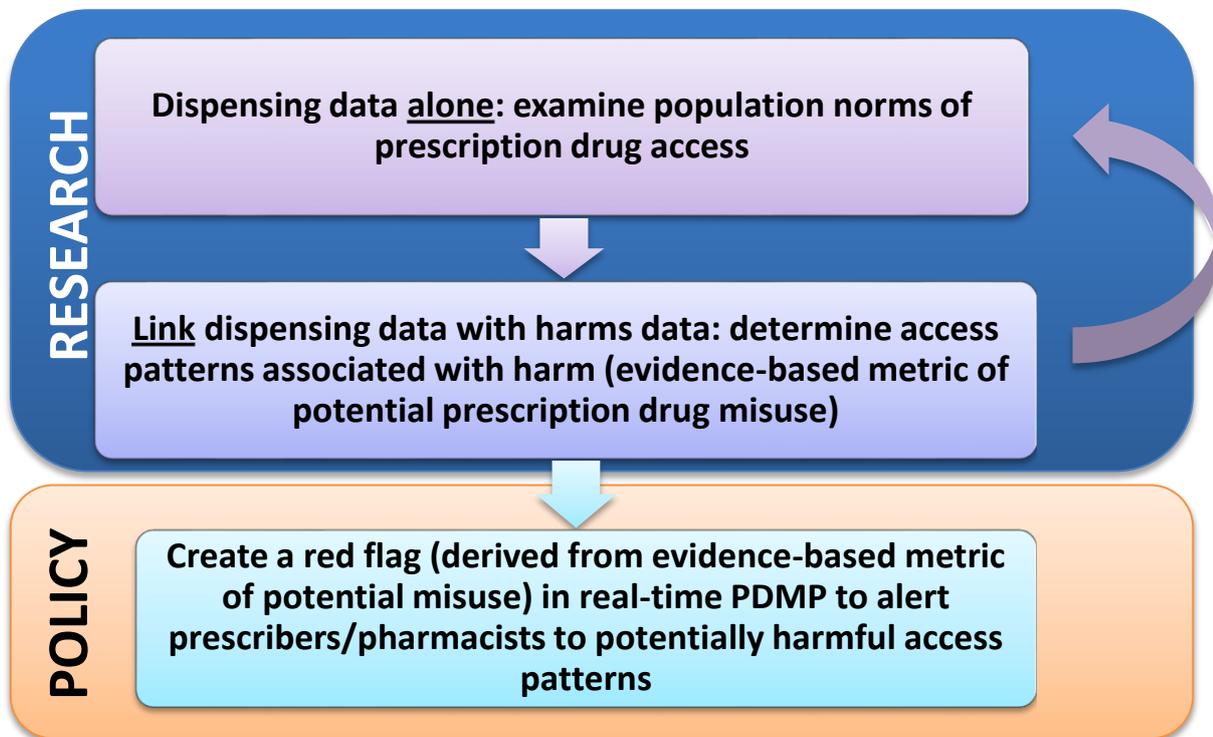
Pharmaceutical claims are the foundation to examine the association between drug exposure, access and harms. In its basic form, pharmaceutical claims alone provide researchers the opportunity to examine population norms of prescription drug access. When linked with outcomes data, such as those described in Table 8.1, researchers have the opportunity to examine associations between drug exposure, access and harms. An evidence-based metric, that is a measure demonstrated to be associated with harm, should then be translated into the PDMP as a red flag, indicating to the prescriber that their patient's access patterns are potentially harmful (Figure 8.1).

This approach allows prescribers the opportunity to identify high-risk individuals, discuss their prescription drug use and potentially stop harms from occurring. Researchers should routinely re-examine pharmaceutical claims data to determine if access patterns shift due to real world events such as prescription drug access policies, listing new prescription drugs on the formulary and/or changes in the illicit drug supply.

#### *8.4.1 Australian prescription drug monitoring programs*

As of November 2016, Australia has two functioning PDMPs, the national Prescription Shopping Programme (PSP) and the Tasmanian Drugs and Poisons Information System Online Remote Access (DORA).

**Figure 8.1** Implementing evidence-based metrics in prescription drug monitoring programs to identify potentially harmful access patterns



The PSP is a national program aiming to identify persons acquiring more prescription drugs than medically required.<sup>50</sup> However, the PSP uses the traditional threshold approach utilising metrics that have not been validated to identify 'shoppers'. Based on the results of our systematic review, the PSP threshold to identify 'shoppers' are extremely high, within 3 months a person must: 1) visit  $\geq 6$  prescribers; 2) obtain  $\geq 25$  target pharmaceutical benefits (dispensings); or 3) obtain any  $\geq 50$  pharmaceutical benefits (dispensings). As these behaviours are extreme, this definition may be more likely to target diversion rather than misuse, which is supported by the fact that prescription drugs with no known abuse potential are included in the target pharmaceuticals (criteria two).

Two limitations of the PSP include the data being retrospective and reactive. For example, if a prescriber suspects their patient of being a 'shopper' the prescriber must contact the PSP information service to confirm their suspicion. If they are correct PSP administrators send the prescriber their patient's dispensing history current to the last 24 hours, which does not require the patient's consent. If the prescriber is incorrect they are not able to obtain their patient's dispensing history, unless their patient provides consent. As PSP information is not available in real-time it hinders a prescriber's ability to discuss a patient's potentially harmful access patterns, as the necessary dispensing history cannot be obtained within the time constraints of a clinical consultation.

On the other hand, DORA is a state-based system operating in Tasmania and allows prescribers and pharmacists real-time access to a patient's dispensing history for prescription drugs with high abuse potential (known as Schedule 8 controlled drugs) which includes opioids and alprazolam.<sup>51</sup> However, as there has been limited peer-reviewed

literature examining the impact of PDMPs, their effect on prescription drug use, misuse or diversion is largely unknown.

In the future, Australia may adopt a national PDMP allowing prescribers and pharmacists' real-time access to patient dispensing histories. In the short term, researchers should examine access patterns for prescription drugs and associations between access and harms. Eventually, this information could be translated into a PDMP as a red flag to better target populations at risk for prescription drug related harms. This proposal is challenging and would require co-ordination at the Commonwealth level, but would provide the opportunity for Australia to be world leaders in examining norms of prescription drug use and quantifying potential misuse.

## **8.5 Conclusions**

There is widespread global concern about the increase in prescription drug use, misuse and harm, particularly in relation to opioid analgesics. Regulatory bodies, third party payers and clinicians are all attempting to balance the provision of safe and effective treatment to those in need while restricting access to those who will derive no benefit or potentially experience harm. This is a complex problem requiring multi-faceted solutions that need to be nuanced to account for local health care delivery models and patient and prescriber behaviour.

Leveraging from large-scale data to conduct post-market surveillance studies of prescription drug access and associated harms forms one important component to drive evidence-based policy responses. However, research of this kind is still relatively under-developed and

methods are far from harmonised. In Australia, our federated model has particularly impeded this effort, where essential data to undertake this work lies in different jurisdictions. To date, the evidence-base relating to prescription drug access patterns and associated benefits and harms is grossly inadequate to drive evidence-based interventions.

While the world has become increasingly digitised and we generate data about every aspect of our lives, it is clear, particularly in Australia, that we are still not making best use of the health information that we currently have to provide timely and robust evidence for policy and clinical decisions. This is an important and fundamental step to ensure individual and societal benefits for the very large and ever-increasing global investment in prescription drugs.

## 8.6 References

1. Pearson SA, Pesa N, Langton JM, Drew A, Faedo M, et al. Studies using Australia's Pharmaceutical Benefits Scheme data for pharmacoepidemiological research: a systematic review of the published literature (1987–2013). *Pharmacoepidemiol Drug Saf.* 2015; 24(5): 447-455.
2. Australian Institute of Health and Welfare. Data linking. 2016; <http://www.aihw.gov.au/data-linking/>. Accessed 23 October 2016.
3. Spilsbury K, Rosman D, Alan J, Boyd JH, Ferrante AM, et al. Cross-border hospital use: analysis using data linkage across four Australian states. *Med J Aust.* 2015; 202(11): 582-586.
4. Australian Government Department of Health. Section 100 - Highly Specialised Drugs Program. 2015; <https://www.pbs.gov.au/info/browse/section-100/s100-highly-specialised-drugs>. Accessed 17 September 2016.
5. Centre for Health Record Linkage. Data dictionaries. 2016; <http://www.cherel.org.au/data-dictionaries-section1>. Accessed 1 September 2016.
6. Australian Government Department of Health. Medicare Benefits Schedule. 2011; <http://www.health.gov.au/internet/hta/publishing.nsf/Content/mbs-1>. Accessed 17 August 2016.
7. Martyres RF, Clode D, Burns JM. Seeking drugs or seeking help? Escalating "doctor shopping" by young heroin users before fatal overdose. *Med J Aust.* 2004; 180(5): 211-214.
8. Baumblatt J, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, et al. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. *JAMA Intern Med.* 2014; 174(5): 796-801.

9. Bohnert AB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011; 305(13): 1315-1321.
10. Bohnert AS, Ilgen MA, Trafton JA, Kerns RD, Eisenberg A, et al. Trends and regional variation in opioid overdose mortality among Veterans Health Administration patients, fiscal year 2001 to 2009. *Clin J Pain*. 2014; 30(7): 605-612.
11. Braden J, Russo J, Fan M, Edlund MJ, Martin BC, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med*. 2010; 170(16): 1425-1432.
12. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, et al. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med*. 2016; 17(1): 85-98.
13. Dhalla IA, Mamdani MM, Sivilotti MLA, Kopp A, Qureshi O, et al. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ*. 2009; 181(12): 891-896.
14. Dunn KM, Saunders KW, Rutter CM, Banta-Gree CJ, Merrill JO, et al. Opioid prescriptions for chronic pain and overdose: a cohort study.[Summary for patients in *Ann Intern Med*. 2010 Jan 19;152(2):l-42; PMID: 20083811]. *Ann Intern Med*. 2010; 152(2): 85-92.
15. Franklin GM, Mai J, Turner J, Sullivan M, Wickizer T, et al. Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline. *Am J Ind Med*. 2012; 55(4): 325-331.

16. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011; 171(7): 686-691.
17. Jena AB, Goldman D, Weaver L, Karaca-Mandic P. Opioid prescribing by multiple providers in Medicare: retrospective observational study of insurance claims. *BMJ.* 2014; 348: g1393.
18. Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, et al. Sex differences in dose escalation and overdose death during chronic opioid therapy: a population-based cohort study. *PLoS One.* 2015; 10(8): e0134550.
19. Miller M, Barber CW, Leatherman S, Fonda J, Hermos JA, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med.* 2015; 175(4): 608-615.
20. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ.* 2015; 350: h2698.
21. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, et al. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med.* 2012; 13(1): 87-95.
22. Rice JB, White AG, Birnbaum HG, Schiller M, Brown DA, et al. A model to identify patients at risk for prescription opioid abuse, dependence, and misuse. *Pain Med.* 2012; 13(9): 1162-1173.
23. Rönkä S, Karjalainen K, Vuori E, Mäkelä P. Personally prescribed psychoactive drugs in overdose deaths among drug abusers: a retrospective register study. *Drug Alcohol Rev.* 2015; 34(1): 82-89.

24. White AG, Birnbaum HG, Schiller M, Tang J, Katz NP. Analytic models to identify patients at risk for prescription opioid abuse. *Am J Manag Care*. 2009; 15(12): 897-906.
25. Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? *Pain*. 2011; 152(7): 1555-1561.
26. Buurma H, Bouvy M, De Smet P, Floor-Schreudering A, Leufkens H, et al. Prevalence and determinants of pharmacy shopping behaviour. *J Clin Pharm Ther*. 2008; 33(1): 17-23.
27. Australian Government Department of Health. Pharmaceutical Benefits Scheme collection of under co-payment data. 2016; <http://www.pbs.gov.au/info/statistics/under-co-payment/under-co-payment-data>. Accessed 30 September 2016.
28. Australian Government Department of Health. Report on the collection of under co-payment data 2014-2015. 2016; <http://www.pbs.gov.au/info/statistics/under-co-payment/ucp-data-report>. Accessed 30 September 2016.
29. Australian Government Department of Human Services. Prescribing in public hospitals participating in the Pharmaceutical Reforms. 2016; <http://medicareaust.com/Accessible/PBS/PrescribinginPublicHospitals/WCAGWelcome/index.html>. Accessed 18 September 2016.
30. Karanges EA, Blanch B, Buckley NA, Pearson SA. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. *Br J Clin Pharm*. 2016; 82(1): 255-267.

31. Kux L. Postmarketing requirements for the class-wide extended-release/long-acting opioid analgesics; public meeting; request for comments. *Fed Regist.* 2014; 79(77): 22499-22501.
32. O'Kane N, Hallvik SE, Marino M, Van Otterloo J, Hildebran C, et al. Preparing a prescription drug monitoring program data set for research purposes. *Pharmacoepidemiol Drug Saf.* 2016; 25(9): 993-997.
33. Furlan AD, MacDougall P, Pellerin D, Shaw K, Spitzig D, et al. Overview of four prescription monitoring/review programs in Canada. *Pain Res Manag.* 2014; 19(2): 102-106.
34. Gugelmann HM, Perrone J. Can prescription drug monitoring programs help limit opioid abuse? *JAMA.* 2011; 306(20): 2258-2259.
35. Haffajee RL, Jena AB, Weiner SG. Mandatory use of prescription drug monitoring programs. *JAMA.* 2015; 313(9): 891-892.
36. Nielsen S, Barratt MJ. Prescription drug misuse: Is technology friend or foe? *Drug Alcohol Rev.* 2009; 28(1): 81-86.
37. Worley J. Prescription drug monitoring programs, a response to doctor shopping: purpose, effectiveness, and directions for future research. *Issues Ment Health Nurs.* 2012; 33(5): 319-328.
38. Bao Y, Pan Y, Taylor A, Radakrishnan S, Luo F, et al. Prescription drug monitoring programs are associated with sustained reductions in opioid prescribing by physicians. *Health Aff (Millwood).* 2016; 35(6): 1045-1051.
39. Gilson AM, Fishman SM, Wilsey BL, Casamalhuapa C, Baxi H. Time series analysis of California's prescription monitoring program: impact on prescribing and multiple provider episodes. *J Pain.* 2012; 13(2): 103-111.

40. Ringwalt C, Garrettson M, Alexandridis A. The effects of North Carolina's prescription drug monitoring program on the prescribing behaviors of the state's providers. *J Prim Prev.* 2014; 36(2): 1-7.
41. McCall III KL, Tu C, Lacroix M, Holt C, Wallace KL, Balk J. Controlled substance prescribing trends and physician and pharmacy utilization patterns: epidemiological analysis of the maine prescription monitoring program from 2006 to 2010. *J Subst Use.* 2013; 18(6): 467-475.
42. Katz N, Panas L, Kim M, Audet AD, Bilansky A, et al. Usefulness of prescription monitoring programs for surveillance—analysis of Schedule II opioid prescription data in Massachusetts, 1996–2006. *Pharmacoepidemiol Drug Saf.* 2010; 19(2): 115-123.
43. Gomes T, Juurlink D, Yao Z, Camacho X, Paterson JM, et al. Impact of legislation and a prescription monitoring program on the prevalence of potentially inappropriate prescriptions for monitored drugs in Ontario: a time series analysis. *CMAJ Open.* 2014; 2(4): E256-E261.
44. Pradel V, Frauger E, Thirion X, Ronfle E, Lapierre V, et al. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. *Pharmacoepidemiol Drug Saf.* 2009; 18(1): 36-43.
45. Reifler LM, Droz D, Bailey JE, Schnoll SH, Fant R, et al. Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain Med.* 2012; 13(3): 434-442.
46. Delcher C, Wagenaar AC, Goldberger BA, Cook RL, Maldonado-Molina MM. Abrupt decline in oxycodone-caused mortality after implementation of Florida's prescription drug monitoring program. *Drug Alcohol Depend.* 2015; 150: 63-68.

47. Patrick SW, Fry CE, Jones TF, Buntin MB. Implementation of prescription drug monitoring programs associated with reductions in opioid-related death rates. *Health Aff (Millwood)*. 2016; 35(7): 1324-1332.
48. Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. *Pain Med*. 2011; 12(5): 747-754.
49. Perrone J, Nelson LS. Medication reconciliation for controlled substances—an “ideal” prescription-drug monitoring program. *New Engl J Med*. 2012;366(25):2341-2343.
50. Australian Government Department of Human Services. Prescription Shopping Programme. 2016; <https://www.humanservices.gov.au/health-professionals/services/medicare/prescription-shopping-programme>. Accessed 7 August 2016.
51. Public Health Services Pharmaceutical Services Branch. DORA – Drugs and Poisons Information System Online Remote Access. 2015; [http://www.dhhs.tas.gov.au/\\_data/assets/pdf\\_file/0012/203430/DORA\\_Info\\_Sheet\\_September\\_2015\\_3.pdf](http://www.dhhs.tas.gov.au/_data/assets/pdf_file/0012/203430/DORA_Info_Sheet_September_2015_3.pdf). Accessed 18 September 2016.

## ***APPENDIX A: Chapter Two Supplementary Material***

### **Chapter Two Supplementary Material**

#### **Contents Page for Supplementary Material**

<b>Title of Supplementary Material</b>	<b>Page Numbers</b>
<b>Supplementary Material 2.1</b> Detailed search strategies executed in systematic review	262
<b>Supplementary Material 2.2</b> 5-item eligibility criteria tool	269
<b>Supplementary Material 2.3</b> Data extraction tool for included studies	270
<b>Electronic Supplementary Material 2.4</b> A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist	276
<b>Supplementary Material 2.5</b> Reference list of excluded studies (N=229)	281
<b>Supplementary Material 2.6</b> Reference list of included studies (N=52)	296
<b>Supplementary Material 2.7</b> Summary of included studies (N=52)	300
<b>Supplementary Material 2.8</b> The reported extent of prescription drug misuse based on indicators with a defined threshold	340
<b>Supplementary Material 2.9</b> The proportion of prescription drugs dispensed to a misuse cohort: determined by a measure of misuse with a defined threshold	348

**Supplementary Material 2.1** Detailed search strategies executed in systematic review

<b>1. MEDLINE Search Strategy (N=5,136)<sup>a</sup></b>			
<i>1. Prescription drug or substance abuse related term</i>	<i>2. Epidemiology and related methods term</i>	<i>3. Routinely collected data</i>	<i>4. A prescription drug misuse-related keyword</i>
Central nervous system agents <sup>b</sup>	Pharmacoepidemiology	Pharmacovigilance	Addic*
Benzodiazepines	Epidemiology	Insurance, health	Abus*
Substance related disorders	Product surveillance, postmarketing	Universal coverage	Misus*
Substance abuse detection	Epidemiological methods	National health programs	Devian*
Polypharmacy	Physician's practice patterns	Health benefit plans, employees	Aberran*
Pharmaceutical services	Drug utilization	Insurance, health, reimbursement	Depend*
Prescription drug misuse	Health services	Centers for Medicare and Medicaid Services	Nonmed*
Prescription drugs	Health services accessibility	Medicaid	Diver*
Drug prescriptions	Public health	Databases, factual	Seek*
	Population surveillance	Insurance coverage	Inapprop*
	Cohort studies	Insurance benefits	Problem*
	Retrospective studies	Single-payer system	Illeg*
	Health services misuse	Reimbursement, incentive	Poison*
		Registries	Selfmed*
		Pharmacies	Inject*
		Drug and narcotic control	Suicid*
		Drug monitoring	Repeat*
		Keywords: Claim* or reimburs*	Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

<sup>a</sup> For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

<sup>b</sup> The subject heading 'central nervous system agents' captures the majority of drug classes associated with misuse. For each search strategy we list any drug class(es) (as subject heading[s]) not captured by 'central nervous system agents'.

<b>2. EMBASE Search Strategy (N=6,160) <sup>a</sup></b>			
<i>1. Prescription drug or substance abuse related term</i>	<i>2. Epidemiology and related methods term</i>	<i>3. Routinely collected data</i>	<i>4. A prescription drug misuse-related keyword</i>
Central nervous system agents	Epidemiology	Government	Addic*
Benzodiazepine	Postmarketing surveillance	Insurance	Abus*
Psychotropic agent	Retrospective study	Factual database	Misus*
Central stimulant agent	Drug utilization	Reimbursement	Devian*
Drug dependence	Health care facility	Drug control	Aberran*
Prescription	Health care	Register	Depend*
Polypharmacy	Health service		Nonmed*
Prescription drug	Drug surveillance program		Diver*
Pharmaceutics	Public health		Seek*
Narcotic analgesic agent	Cohort analysis		Inapprop*
			Problem*
			Illeg*
			Poison*
			Selfmed*
			Inject*
			Suicid*
			Repeat*
			Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

<sup>a</sup> For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

<b>3. CINAHL Search Strategy (N=471) <sup>a</sup></b>			
<i>1. Prescription drug or substance abuse related term</i>	<i>2. Epidemiology and related methods term</i>	<i>3. Routinely collected data</i>	<i>4. A prescription drug misuse-related keyword</i>
Central nervous system agents	Epidemiology	Insurance, pharmaceutical services	Addic*
Substance use disorders	Epidemiological research	Insurance, health reimbursement	Abus*
Substance abuse detection	Disease surveillance	Insurance, health	Misus*
Polypharmacy	Population surveillance	Insurance benefits	Devian*
Drug dependence	Product surveillance	Insurance coverage	Aberran*
Prescriptions, drug	Drug utilization	Resource databases, health	Depend*
Drugs, prescription	Health resource utilization	Databases, health	Nonmed*
	Practice patterns	Medicaid	Diver*
	Prescribing patterns	United States Centers for Medicare and Medicaid services	Seek*
	Pharmacy service	Medicare	Inapprop*
	Pharmacy and pharmacology	Insurance, Medigap	Problem*
	Public health	Pharmacovigilance	Illeg*
	Retrospective design	Student health services	Poison*
	Health services misuse	Reimbursement, incentive	Selfmed*
	Inappropriate prescribing	Drug monitoring	Inject*
		Key words: Claim* or reimburse*	Suicid*
			Repeat*
			Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

<sup>a</sup> For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

<b>4. MEDLINE In Process Search Strategy (N=896)<sup>a</sup></b>			
<i>1. Prescription drug or substance abuse related term</i>	<i>2. Epidemiology and related methods term</i>	<i>3. Routinely collected data</i>	<i>4. A prescription drug misuse-related keyword</i>
Benzodiazepine*	Epidemiol*	Monitor*	Addic*
Prescri*	Pharmacoepi*	Reimburs*	Abus*
Analgesic*	Cohort*	Claim*	Misus*
Opioid*	Retro*	Benefit*	Devian*
Medication*	Population*	Data*	Aberran*
Stimulant*			Depend*
Antidepressant*			Nonmed*
Anipsychotic*			Diver*
Polypharmacy*			Seek*
			Inapprop*
			Problem*
			Illeg*
			Poison*
			Selfmed*
			Inject*
			Suicid*
			Repeat*
			Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

<sup>a</sup> For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

<b>5. Google Scholar Search Strategy (N=600)<sup>a</sup></b>
"Prescription drug" + excess
"Prescription drug" + misuse
"Prescription drug" + abuse

<sup>a</sup> Reviewed first 200 results per search

## Supplementary Material 2.2 5-item eligibility criteria tool

### Initial cover sheet SYSTEMATIC REVIEW: Prescription drug misuse

REVIEWER INITIALS: \_\_\_\_\_

1a. First author, year of publication and setting:	
1b. Study observation period (s):	
1c. Prescription medicines included in study (list all):	<b>If no, prescribed medicine:</b> <input type="checkbox"/> illicit drugs only <input type="checkbox"/> OTC only
2. Is the article original research? <input type="checkbox"/> yes <input type="checkbox"/> no <b>If no, please circle article type:</b> Review Letter to the editor Editorial Conference abstract	
3. Is the study written in English, and published between 2000 and 2013? <input type="checkbox"/> yes <input type="checkbox"/> no	
4a. Does the study measure prescribed medicine use from a routinely collected data source? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unclear	
Prescription data source details: Type of dataset utilised: <input type="checkbox"/> dispensing/claims <input type="checkbox"/> prescription <input type="checkbox"/> other, specify: _____ Dataset name and location: _____	
<i>If yes to 4a—</i> 4b. Is there at least one outcome reporting prescription drug misuse using the data source identified in 4a? <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unclear	
5. Does the population include adults? <input type="checkbox"/> yes <input type="checkbox"/> no	
⇒ Should the study be included? If 2-5 are all "yes" <input type="checkbox"/> definite If any of 2-5 are "no" <input type="checkbox"/> exclude If any are "unclear" <input type="checkbox"/> probable	
If article is excluded: <input type="checkbox"/> Consult during write-up of systematic review (i.e. relevant findings or theory) <input type="checkbox"/> Read back references (tick if article included a measure of problematic use of medicine but excluded)	
Inclusion Criteria: <ul style="list-style-type: none"><li>• Study includes at least one prescribed medicine</li><li>• Reports an outcome related to prescription drug misuse</li><li>• Routinely collected data is study source for prescribed medicine (s)</li><li>• Published between 2000-2013</li><li>• English language</li></ul>	

## Supplementary Material 2.3 Data extraction tool for included studies

SYSTEMATIC REVIEW : Prescription drug misuse	
Main Data Extraction Tool	
Reviewer initials: _____	Journal name: _____
<b>1. Bibliographic and study details</b>	
First author surname (year): _____ Study funding source: <input type="checkbox"/> Grant (gvt/research) <input type="checkbox"/> Industry (Health insurance or pharmaceutical) <input type="checkbox"/> No funding <input type="checkbox"/> Not recorded/specified <input type="checkbox"/> Other, please specify: _____	
Study location (continent): <input type="checkbox"/> Asia <input type="checkbox"/> Africa <input type="checkbox"/> North America <input type="checkbox"/> South America <input type="checkbox"/> Europe <input type="checkbox"/> Australia	
Further location details specified (i.e. country and/or states included in study): _____	
_____	
<b>2. Study focus and aims</b>	
Reported aim of study (verbatim): _____	
_____	
_____	
Prescribed medicine class(es) of interest (tick all that apply): <input type="checkbox"/> Antipsychotic <input type="checkbox"/> Antidepressant <input type="checkbox"/> Benzodiazepine	
<input type="checkbox"/> Diuretic <input type="checkbox"/> Opioid <input type="checkbox"/> Central nervous system stimulant <input type="checkbox"/> Other medicine class _____	
Number of unique medicines investigated in article: <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> ≥5 <input type="checkbox"/> Class not further specified <input type="checkbox"/> Medicines not specified. Specify the generic name of each medicine investigated: _____	
_____	
_____	
<b>3. Study period, data and cohort details</b>	
First year of observation: _____ Last year of observation: _____ Longest period of observation: _____ months	
<u>Data details</u> (not cohort specific)	
Number of datasets used to measure outcomes: _____ datasets	
Data set or source 1 (name and type, i.e. medicine dispensing data): _____	
Number of persons covered by the dataset: _____ people OR Population of region: _____	
Percentage of the population covered by the dataset: _____ %	
Population insured/covered by the dataset (e.g. age, employed, role, location etc)	
_____	
_____	
Data set or source 2 (name and type, i.e. medicine dispensing data): _____	
Number of persons covered by the dataset: _____ people OR Population of region: _____	
Percentage of the population covered by the dataset: _____ %	
Population insured/covered by the dataset (e.g. age, employed, role, location etc)	
_____	
_____	

Cohort details

Number of cohorts of interest specified (including any comparison groups): \_\_\_\_\_ cohorts

Prescription drug misuse term used in manuscript (i.e. misuse, abuse, deviant etc): \_\_\_\_\_

Coverage of data:  National  State/province/region specific  Multiple states/provinces/regions included, number: \_\_\_\_\_

Cohort 1 (name): \_\_\_\_\_

Cohort definition:  Prescription/dispensing of medicine OR  Pre-defined abuse cohort only

Cohort of interest inclusion criteria: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Cohort of interest exclusion criteria: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Number of persons identified in cohort (%): \_\_\_\_\_ Mean age (SD): \_\_\_\_\_ Median age (range): \_\_\_\_\_

Cohort 2 (name): \_\_\_\_\_

Cohort definition:  Prescription/dispensing of medicine OR  Pre-defined abuse cohort only

Cohort of interest inclusion criteria: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Cohort of interest exclusion criteria: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Number of persons identified in cohort (%): \_\_\_\_\_ Mean age (SD): \_\_\_\_\_ Median age (range): \_\_\_\_\_

Cohort 3 (name): \_\_\_\_\_

Cohort definition:  Prescription/dispensing of medicine OR  Pre-defined abuse cohort only

Cohort of interest inclusion criteria: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Cohort of interest exclusion criteria: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Number of persons identified in cohort(%): \_\_\_\_\_ Mean age (SD): \_\_\_\_\_ Median age (range): \_\_\_\_\_

4. Misuse outcomes			
Outcome 1	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	<input type="checkbox"/> Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	<input type="checkbox"/> Number of prescribing doctors		
	<input type="checkbox"/> Amount dispensed/prescribed (i.e. DDD)		
	<input type="checkbox"/> Number of prescriptions		
	<input type="checkbox"/> Specific medicine or combination: specify _____ _____		
	<input type="checkbox"/> Overlapping prescriptions		
	<input type="checkbox"/> Other: specify _____ _____ _____		
Outcome 2	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	<input type="checkbox"/> Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	<input type="checkbox"/> Number of prescribing doctors		
	<input type="checkbox"/> Amount dispensed/prescribed (i.e. DDD)		
	<input type="checkbox"/> Number of prescriptions		
	<input type="checkbox"/> Specific medicine or combination: specify _____ _____		
	<input type="checkbox"/> Overlapping prescriptions		
	<input type="checkbox"/> Other: specify _____ _____ _____		

Outcome 3	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	<input type="checkbox"/> Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	<input type="checkbox"/> Number of prescribing doctors		
	<input type="checkbox"/> Amount dispensed/prescribed (i.e. DDD)		
	<input type="checkbox"/> Number of prescriptions		
	<input type="checkbox"/> Specific medicine or combination: specify _____ _____		
	<input type="checkbox"/> Overlapping prescriptions		
	<input type="checkbox"/> Other: specify _____ _____ _____		
Outcome 4	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	<input type="checkbox"/> Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	<input type="checkbox"/> Number of prescribing doctors		
	<input type="checkbox"/> Amount dispensed/prescribed (i.e. DDD)		
	<input type="checkbox"/> Number of prescriptions		
	<input type="checkbox"/> Specific medicine or combination: specify _____ _____		
	<input type="checkbox"/> Overlapping prescriptions		
	<input type="checkbox"/> Other: specify _____ _____ _____		

Outcome 5	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	<input type="checkbox"/> Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	<input type="checkbox"/> Number of prescribing doctors		
	<input type="checkbox"/> Amount dispensed/prescribed (i.e. DDD)		
	<input type="checkbox"/> Number of prescriptions		
	<input type="checkbox"/> Specific medicine or combination: specify _____ _____		
	<input type="checkbox"/> Overlapping prescriptions		
	<input type="checkbox"/> Other: specify _____ _____ _____		

Other relevant reported trends/outcomes related to cohort of interest:

Describe other outcome(s) measured	Report finding(s) related to other outcome(s)



**Supplementary Material 2.4** A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

**Supplementary Material 2.4A:** A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist

Section/topic	#	Checklist item	Reported on page #	Comments
<b>INTRODUCTION</b>				
Was an “a priori” design provided?	1	The research question and inclusion criteria should be established before the conduct of the review.	58	
<b>METHODS</b>				
Was there duplicate study selection and data extraction?	2	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	59	
Was a comprehensive literature search performed?	3	At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialised registers, or experts in the particular field of study, and by reviewing the references in the studies found.	59, SM 1	
Was the status of publication (i.e., grey literature) used as an inclusion criterion?	4	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	58, 75	
Were the methods used to combine the findings of studies	5	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I <sup>2</sup> ). If heterogeneity exists, a random effects model should be used and/or the clinical	X	Not a meta-analysis: qualitative synthesis

appropriate?		appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).		
<b>RESULTS</b>				
Were the characteristics of the included studies provided?	6	In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analysed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Tables 2.1 and 2.2	
Was the scientific quality of the included studies assessed and documented?	7	“A priori” methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	73	
Was the scientific quality of the included studies used appropriately in formulating conclusions?	8	The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	X	Not a meta-analysis: qualitative synthesis
Was the likelihood of publication bias assessed?	9	An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	X	Not a meta-analysis: qualitative synthesis
<b>FUNDING</b>				
Was the conflict of interest included?	10	Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	73, Table 2.1, 257-258	
<b>APPENDIX</b>				
Was a list of studies (included and excluded) provided?	11	A list of included and excluded studies should be provided.	SM 5 and 6	

**Supplementary Material 2.4B:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #	Comments
<b>TITLE</b>				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	53	
<b>ABSTRACT</b>				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	55-56	No registration number
<b>INTRODUCTION</b>				
Rationale	3	Describe the rationale for the review in the context of what is already known.	57-58	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	58	
<b>METHODS</b>				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X	No registered protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	58	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	59	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	SM 1	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	58-59	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	59-61, SM 2 and 3	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	59-61, SM 3	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	X	Not a meta-analysis: qualitative synthesis
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	59-61	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	61	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	X	Not a meta-analysis: qualitative synthesis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	X	Not a meta-analysis: qualitative synthesis
<b>RESULTS</b>				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	62, Figure 2.1	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	SM 7	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	X	Not a meta-analysis: qualitative synthesis
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	SM 7	Not a meta-analysis: qualitative synthesis
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	62-73	

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	73	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	X	Not a meta-analysis: qualitative synthesis
<b>DISCUSSION</b>				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	73-77	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	75-76	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	77	
<b>FUNDING</b>				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	257-258	

## Supplementary Material 2.5 Reference list of excluded studies (N=229)

1. Aeschbach Jachmann C, Jagsch R, Winklbaier B, Matzenauer C, Fischer G. Office-based treatment in opioid dependence: A critical survey of prescription practices for opioid maintenance medications and concomitant benzodiazepines in Vienna, Austria. *European Addiction Research* 2008;**14**(4):206-212.
2. Akincigil A, Bowblis JR, Levin C, Walkup JT, Jan S, Crystal S. Adherence to antidepressant treatment among privately insured patients diagnosed with depression. *Medical Care* 2007;**45**(4):363-9.
3. Albsoul-Younes A, Wazaify M, Yousef A-M, Tahaine L. Abuse and misuse of prescription and nonprescription drugs sold in community pharmacies in Jordan. *Substance Use & Misuse* 2010;**45**(9):1319-29.
4. Almarsdottir AB, Grimsson A. Over-the-counter codeine use in Iceland: the impact of increased access. *Scandinavian Journal of Public Health* 2000;**28**(4):270-4.
5. Al-Omar HA, Al-Sultan MS, Abu-Auda HS. Prescribing of potentially inappropriate medications among the elderly population in an ambulatory care setting in a Saudi military hospital: Trend and cost. *Geriatrics & Gerontology International* 2013;**13**(3):616-21.
6. Andersson K, Melander A, Svensson C, Lind O, Nilsson JLG. Repeat prescriptions: refill adherence in relation to patient and prescriber characteristics, reimbursement level and type of medication. *European Journal of Public Health* 2005;**15**(6):621-6.
7. Andrade SE, Raebel MA, Morse AN, Davis RL, Chan KA, Finkelstein JA, Fortman KK, McPhillips H, Roblin D, Smith DH, Yood MU, Platt R, H Gurwitz J. Use of prescription medications with a potential for fetal harm among pregnant women. *Pharmacoepidemiology & Drug Safety* 2006;**15**(8):546-54.
8. Arendt M, Munk-Jorgensen P, Sher L, Jensen SOW. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up study of Danish substance users in treatment. *Drug & Alcohol Dependence* 2011;**114**(2-3):134-9.
9. Arendt M, Munk-Jorgensen P, Sher L, Jensen SOW. Mortality following treatment for cannabis use disorders: Predictors and causes. *Journal of Substance Abuse Treatment* 2013;**44**(4):400-406.
10. Arfken CL, Schuster CR, Johanson CE. Postmarketing surveillance of abuse liability of sibutramine. *Drug and Alcohol Dependence* 2003;**69**(2):169-173.
11. Azemi M, Berisha M, Kolgeci S, Bejiqi R. Frequency, etiology and several sociodemographic characteristics of acute poisoning in children treated in the intensive care unit. *Materia Sociomedica* 2012;**24**(2):76-80.
12. Bachs LC, Engeland A, Morland JG, Skurtveit S. The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. *Clin Pharmacol Ther* 2009;**85**(6):596-9.
13. Baehren DF, Marco CA, Droz DE, Sinha S, Callan EM, Akpunonu P. A statewide prescription monitoring program affects emergency department prescribing behaviors. *Annals of Emergency Medicine* 2010;**56**(1):19-23.e1-3.
14. Balfour JE, O'Rourke N. Older adults with Alzheimer disease, comorbid arthritis and prescription of psychotropic medications. *Pain Research and Management* 2003;**8**(4):198-204.

15. Bali V, Raisch DW, Moffett ML, Khan N. Determinants of nonmedical use, abuse or dependence on prescription drugs, and use of substance abuse treatment. *Research In Social & Administrative Pharmacy* 2013;**9**(3):276-87.
16. Balit CR, Isbister GK, Peat J, Dawson AH, Whyte IM. Paracetamol recall: a natural experiment influencing analgesic poisoning. *Medical Journal of Australia* 2002;**176**(4):162-5.
17. Balkrishnan R, Byerly WG, Camacho FT, Shrestha A, Anderson RT. Effect of prescription benefit changes on medical care utilization in a Medicare HMO population. *American Journal of Managed Care* 2001;**7**(11):1093-1100.
18. Ball DE, Taderera A. Development of drug use indicators for epilepsy. *Central African Journal of Medicine* 2003;**49**(11-12):134-8.
19. Banken JA, Foster H. Dextromethorphan. *Annals of the New York Academy of Sciences* 2008;**1139**:402-11.
20. Barbui C, Nose M, Rambaldelli G, Bonetto C, Levi D, Patten SB, Tansella M, Amaddeo F, Androne N, Barlocco L, Bianco M, Celani D, Cipriani A, Colombo P, Giaroli G, Gregis M, Grosso L, Guarnier C, Latino M, Maggiolo D, Malvini L, Marsilio A, Migliarese G, Moretti F, Nicoli M, Perego G, Pighi C, Pucci C, Salvi G, Stegagno M, Tentoni L, Tosato S, Tournikioti K, Turchetti R, Venturi C, Versace A, Vivenza V, Zambello F. Development of a registry for monitoring psychotropic drug prescriptions: aims, methods and implications for ordinary practice and research. *International Journal of Methods in Psychiatric Research* 2005;**14**(3):151-157.
21. Bargagli AM, Hickman M, Davoli M, Perucci CA, Schifano P, Buster M, Brugal T, Vicente J, Group CE. Drug-related mortality and its impact on adult mortality in eight European countries. *European Journal of Public Health* 2006;**16**(2):198-202.
22. Baser O, Chalk M, Fiellin DA, Gastfriend DR. Cost and utilization outcomes of opioid-dependence treatments. *The American Journal of Managed Care* 2011;**17 Suppl 8**:S235-248.
23. Bateman DN, Gorman DR, Bain M, Inglis JHC, House FR, Murphy D. Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. *British Journal of Clinical Pharmacology* 2006;**62**(5):573-581.
24. Batty GM, Osborne CA, Swift CG, Jackson SH. Development of an indicator to identify inappropriate use of benzodiazepines in elderly medical in-patients. *International Journal of Geriatric Psychiatry* 2000;**15**(10):892-6.
25. Baumevieuille M, Daveluy A, Maurain C, Begaud B, Haramburu F. Medicines submitted to narcotics regulations in France, 1992-2007. *Fundamental & Clinical Pharmacology* 2009;**23**(3):345-9.
26. Baxter JD, Clark RE, Samnaliev M, Leung GY, Hashemi L. Factors associated with Medicaid patients' access to buprenorphine treatment. *Journal of Substance Abuse Treatment* 2011;**41**(1):88-96.
27. Bednall R, McRobbie D, Hicks A. Identification of medication-related attendances at an A & E department. *Journal of Clinical Pharmacy & Therapeutics* 2003;**28**(1):41-5.
28. Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug & Alcohol Dependence* 2009;**104**(1-2):73-7.
29. Bergen H, Hawton K, Kapur N, Cooper J, Steeg S, Ness J, Waters K. Shared characteristics of suicides and other unnatural deaths following non-fatal self-harm?

- A multicentre study of risk factors. *Psychological Medicine* 2012;**42**(4):727-41.
30. Beynon C, Bellis MA, Millar T, Meier P, Thomson R, Mackway Jones K. Hidden need for drug treatment services: measuring levels of problematic drug use in the North West of England. *Journal of Public Health Medicine* 2001;**23**(4):286-91.
  31. Bhalla A, Dutta S, Chakrabarti A. A profile of substance abusers using the emergency services in a tertiary care hospital in Sikkim. *Indian Journal of Psychiatry* 2006;**48**(4):243-7.
  32. Birnbaum HG, White AG, Reynolds JL, Greenberg PE, Zhang M, Vallow S, Schein JR, Katz NP. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. *Clinical Journal of Pain* 2006;**22**(8):667-76.
  33. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Medicine* 2011;**12**(4):657-667.
  34. Bjorn A-MB, Jepsen P, Larsson HJ, Thomsen HF, Kieler H, Ehrenstein V, Christensen S. Hospitalizations for opioid poisoning: a nation-wide population-based study in Denmark, 1998-2004. *Addiction* 2009;**104**(1):104-8.
  35. Blackwell SA, Baugh DK, Ciborowski GM, Montgomery MA. National study of prescription poisoning with psychoactive and nonpsychoactive medications in Medicare/Medicaid dual enrollees age 65 or over. *Journal of Psychoactive Drugs* 2011;**43**(3):229-37.
  36. Bloch-Teitelbaum A, Lude S, Rauber-Luthy C, Kupferschmidt H, Russmann S, Kullak-Ublick GA, Ceschi A. Medication wrong route administration: a poisons center-based study. *Expert Opinion on Drug Safety* 2013;**12**(2):145-52.
  37. Boaz TL, Constantine RJ, Robst J, Becker MA, Howe AM. Risperidone long-acting therapy prescribing patterns and their impact on early discontinuation of treatment in a large Medicaid population. *Journal of Clinical Psychiatry* 2011;**72**(8):1079-85.
  38. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011;**305**(13):1315-21.
  39. Bond C, Matheson C, Williams S, Williams P, Donnan P. Repeat prescribing: a role for community pharmacists in controlling and monitoring repeat prescriptions. *British Journal of General Practice* 2000;**50**(453):271-5.
  40. Bonilha L, Collares CF, do Amaral DA, Dantas Barcia S, de Almeida Oliveira AMA, Li LM. Antiepileptic drugs: a study of 1028 cases registered by the Sao Paulo Intoxication Control Center. *Seizure* 2005;**14**(3):170-4.
  41. Bonuck KA, Memmott MM, Arno PS. Cost-related prescription drug misuse among older persons. *Journal of Research in Pharmaceutical Economics* 2001;**11**(1):39-49.
  42. Boyer EW, Wines JD, Jr. Impact of Internet pharmacy regulation on opioid analgesic availability. *Journal of Studies on Alcohol & Drugs* 2008;**69**(5):703-8.
  43. Braden JB, Fan M-Y, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. *Journal of Pain* 2008;**9**(11):1026-35.
  44. Braden JB, Russo J, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Emergency department visits among recipients of chronic opioid therapy. *Archives of Internal Medicine* 2010;**170**(16):1425-32.
  45. Braker LS, Reese AE, Card RO, Van Howe RS. Screening for potential prescription

- opioid misuse in a Michigan Medicaid population. *Family Medicine* 2009;**41**(10):729-34.
46. Bramness JG, Furu K, Skurtveit S, Engeland A. Effect of the market withdrawal of carisoprodol on use of other prescribed drugs with abuse potential. *Clinical Pharmacology & Therapeutics* 2012;**91**(3):438-41.
  47. Bramness JG, Skurtveit S, Morland J, Engeland A. The risk of traffic accidents after prescriptions of carisoprodol. *Accident; Analysis & Prevention* 2007;**39**(5):1050-5.
  48. Bramness JG, Skurtveit S, Morland J, Engeland A. An increased risk of motor vehicle accidents after prescription of methadone. *Addiction* 2012;**107**(5):967-72.
  49. Bramness JG, Skurtveit S, Neutel CI, Morland J, Engeland A. Minor increase in risk of road traffic accidents after prescriptions of antidepressants: a study of population registry data in Norway. *Journal of Clinical Psychiatry* 2008;**69**(7):1099-103.
  50. Bramness JG, Skurtveit S, Neutel CI, Morland J, Engeland A. An increased risk of road traffic accidents after prescriptions of lithium or valproate? *Pharmacoepidemiology & Drug Safety* 2009;**18**(6):492-6.
  51. Breekveldt-Postma NS, Schillevoort I, Nolen WA, Veraart CPWM, Herings RMC. Selective prescribing of atypical antipsychotics. *Pharmacoepidemiology & Drug Safety* 2005;**14**(1):25-30.
  52. Breen CL, Degenhardt LJ, Bruno RB, Roxburgh AD, Jenkinson R. The effects of restricting publicly subsidised temazepam capsules on benzodiazepine use among injecting drug users in Australia. *Medical Journal of Australia* 2004;**181**(6):300-304.
  53. Brennan PL, Kagay CR, Geppert JJ, Moos RH. Elderly Medicare inpatients with substance use disorders: characteristics and predictors of hospital readmissions over a four-year interval. *Journal of Studies on Alcohol* 2000;**61**(6):891-5.
  54. Brennan PL, Kagay CR, Geppert JJ, Moos RH. Predictors and outcomes of outpatient mental health care: a 4-year prospective study of elderly Medicare patients with substance use disorders. *Medical Care* 2001;**39**(1):39-49.
  55. Briesacher BA, Limcangco MR, Simoni-Wastila L, Doshi JA, Levens SR, Shea DG, Stuart B. The quality of antipsychotic drug prescribing in nursing homes. *Archives of Internal Medicine* 2005;**165**(11):1280-5.
  56. Brinker A, Mosholder A, Schech SD, Burgess M, Avigan M. Indication and use of drug products used to treat attention-deficit/hyperactivity disorder: a cross-sectional study with inference on the likelihood of treatment in adulthood. *Journal of Child & Adolescent Psychopharmacology* 2007;**17**(3):328-33.
  57. Brixner DI, Oderda GM, Roland CL, Rublee DA. Opioid expenditures and utilization in the Medicaid system. *Journal of Pain and Palliative Care Pharmacotherapy* 2006;**20**(1):5-13.
  58. Brownstein JS, Green TC, Cassidy TA, Butler SF. Geographic information systems and pharmacoepidemiology: using spatial cluster detection to monitor local patterns of prescription opioid abuse. *Pharmacoepidemiology & Drug Safety* 2010;**19**(6):627-37.
  59. Bunn TL, Yu L, Spiller HA, Singleton M. Surveillance of methadone-related poisonings in Kentucky using multiple data sources. *Pharmacoepidemiology and Drug Safety* 2010;**19**(2):124-131.
  60. Burns JM, Martyres RF, Clode D, Boldero JM. Overdose in young people using heroin: associations with mental health, prescription drug use and personal circumstances. *Medical Journal of Australia* 2004;**181**(7 Suppl):S25-8.
  61. Busch SH, Frank RG, Leslie DL, Martin A, Rosenheck RA, Martin EG, Barry CL.

- Antidepressants and suicide risk: how did specific information in FDA safety warnings affect treatment patterns? *Psychiatric Services* 2010;**61**(1):11-6.
62. Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduction Journal* 2011;**8**:29.
  63. Butler SF, Black RA, Serrano JMG, Wood ME, Budman SH. Characteristics of prescription opioid abusers in treatment: prescription opioid use history, age, use patterns, and functional severity. *Journal of Opioid Management* 2010;**6**(4):239-41, 246-52.
  64. Butler SF, Budman SH, Licari A, Cassidy TA, Liou K, Dickinson J, Brownstein JS, Benneyan JC, Green TC, Katz N. National addictions vigilance intervention and prevention program (NAVIPPRO): a real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiology & Drug Safety* 2008;**17**(12):1142-54.
  65. Butt AA, Justice AC, Skanderson M, Rigsby MO, Good CB, Kwok CK. Rate and predictors of treatment prescription for hepatitis C. *Gut* 2007;**56**(3):385-389.
  66. Buurma H, Bouvy ML, De Smet PAGM, Floor-Schreuderling A, Leufkens HGM, Egberts ACG. Prevalence and determinants of pharmacy shopping behaviour. *Journal of Clinical Pharmacy & Therapeutics* 2008;**33**(1):17-23.
  67. Calcaterra S, Glanz J, Binswanger IA. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. *Drug & Alcohol Dependence* 2013;**131**(3):263-70.
  68. Callaghan RC, Macdonald SA. Changes in the rates of alcohol- and drug-related hospital separations for Canadian provinces: 1996 to 2005. *Canadian Journal of Public Health. Revue Canadienne de Sante Publique* 2009;**100**(5):393-6.
  69. Candrilli SD, Davis KL, Iyer S. Impact of constipation on opioid use patterns, health care resource utilization, and costs in cancer patients on opioid therapy. *Journal of Pain and Palliative Care Pharmacotherapy* 2009;**23**(3):231-241.
  70. Carise D, Dugosh KL, McLellan AT, Camilleri A, Woody GE, Lynch KG. Prescription OxyContin abuse among patients entering addiction treatment. *American Journal of Psychiatry* 2007;**164**(11):1750-6.
  71. Castelpietra G, Morsanutto A, Pascolo-Fabrici E, Isacson G. Antidepressant use and suicide prevention: a prescription database study in the region Friuli Venezia Giulia, Italy. *Acta Psychiatrica Scandinavica* 2008;**118**(5):382-8.
  72. Chen C-Y, Yeh H-H, Fang S-Y, Wu EC-H, Chang IS, Lin K-M. Overlapping prescriptions of stimulants for children and adolescents with attention-deficit hyperactivity disorder. *Psychiatric Services* 2012;**63**(10):1011-8.
  73. Chen H, Patel A, Sherer J, Aparasu R. The definition and prevalence of pediatric psychotropic polypharmacy. *Psychiatric Services* 2011;**62**(12):1450-5.
  74. Cheng JS, Huang WF, Lin KM, Shih YT. Characteristics associated with benzodiazepine usage in elderly outpatients in Taiwan. *International Journal of Geriatric Psychiatry* 2008;**23**(6):618-624.
  75. Chiroli S, Chinellato A, Didoni G, Mazzi S, Lucioni C. Utilisation pattern of nonspecific nonsteroidal anti-inflammatory drugs and COX-2 inhibitors in a local health service unit in northeast Italy. *Clinical Drug Investigation* 2003;**23**(11):751-60.
  76. Cicero TJ, Wong G, Tian Y, Lynskey M, Todorov A, Isenberg K. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: data

- from an insurance claims database. *Pain* 2009;**144**(1-2):20-27.
77. Cifuentes M, Webster B, Genevay S, Pransky G. The course of opioid prescribing for a new episode of disabling low back pain: opioid features and dose escalation. *Pain* 2010;**151**(1):22-9.
  78. Clark RE, Samnaliev M, McGovern MP. Treatment for co-occurring mental and substance use disorders in five state Medicaid programs. *Psychiatric Services* 2007;**58**(7):942-8.
  79. Cohen SA, Lawson JA, Graudins LV, Pearson S-A, Gazarian M. Changes in anticonvulsant prescribing for Australian children: implications for quality use of medicines. *Journal of Paediatrics & Child Health* 2012;**48**(6):490-5.
  80. Colpaert K, Vanderplasschen W, Broekaert E. Comparison of single and multiple agency clients in substance abuse treatment services. *European Addiction Research* 2007;**13**(3):156-166.
  81. Cook S, Indig D, Gray J, McGrath D. Opiate overdose and health treatment options for opiate users in New South Wales, 1999-2002. *New South Wales Public Health Bulletin* 2004;**15**(7-8):125-131.
  82. Corsenac P, Lagarde E, Gadegbeku B, Delorme B, Tricotel A, Castot A, Moore N, Philip P, Laumon B, Orriols L. Road traffic crashes and prescribed methadone and buprenorphine: a French registry-based case-control study. *Drug & Alcohol Dependence* 2012;**123**(1-3):91-7.
  83. Curtis LH, Ostbye T, Sendersky V, Hutchison S, Allen LaPointe NM, Al-Khatib SM, Usdin Yasuda S, Dans PE, Wright A, Califf RM, Woosley RL, Schulman KA. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *American Journal of Medicine* 2003;**114**(2):135-41.
  84. Davstad I, Allebeck P, Leifman A, Stenbacka M, Romelsjo A. Self-reported drug use and mortality among a nationwide sample of Swedish conscripts - a 35-year follow-up. *Drug and Alcohol Dependence* 2011;**118**(2-3):383-390.
  85. Deck D, Wiitala W, McFarland B, Campbell K, Mullooly J, Krupski A, McCarty D. Medicaid coverage, methadone maintenance, and felony arrests: outcomes of opiate treatment in two states. *Journal of Addictive Diseases* 2009;**28**(2):89-102.
  86. Degenhardt L, Day C, Dietze P, Pointer S, Conroy E, Collins L, Hall W. Effects of a sustained heroin shortage in three Australian States. *Addiction* 2005;**100**(7):908-920.
  87. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug & Alcohol Dependence* 2009;**105**(1-2):9-15.
  88. DeLorenze GN, Satre DD, Quesenberry CP, Tsai A, Weisner CM. Mortality after diagnosis of psychiatric disorders and co-occurring substance use disorders among HIV-infected patients. *AIDS Patient Care & Stds* 2010;**24**(11):705-712.
  89. Devarajah S, Sullivan JV, Purcell A, Tutty S, Sinha C, Lindow SW. Methadone use in pregnancy: evidence of progression in the severity of addiction. *Journal of Obstetrics & Gynaecology* 2012;**32**(8):753-5.
  90. Dhalla IA, Mamdani MM, Gomes T, Juurlink DN. Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario. *Canadian Family Physician* 2011;**57**(3):e92-6.
  91. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ Canadian Medical Association Journal* 2009;**181**(12):891-6.

92. Dosreis S, Yoon Y, Rubin DM, Riddle MA, Noll E, Rothbard A. Antipsychotic treatment among youth in foster care. *Pediatrics* 2011;**128**(6):e1459-66.
93. Dosreis S, Zito JM, Safer DJ, Gardner JF, Puccia KB, Owens PL. Multiple psychotropic medication use for youths: a two-state comparison. *Journal of Child and Adolescent Psychopharmacology* 2005;**15**(1):68-77.
94. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of Internal Medicine* 2010;**152**(2):85-92.
95. Edlund MJ, Martin BC, Devries A, Fan M-Y, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *Clinical Journal of Pain* 2010;**26**(1):1-8.
96. Edlund MJ, Martin BC, Fan MY, Braden JB, Devries A, Sullivan MD. An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. *Journal of Pain and Symptom Management* 2010;**40**(2):279-289.
97. Edlund MJ, Martin BC, Fan M-Y, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. *Drug & Alcohol Dependence* 2010;**112**(1-2):90-8.
98. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain* 2007;**129**(3):355-62.
99. El-Aneed A, Alaghebandan R, Gladney N, Collins K, MacDonald D, Fischer B. Prescription drug abuse and methods of diversion: the potential role of a pharmacy network. *Journal of Substance Use* 2009;**14**:75-83.
100. Engeland A, Skurtveit S, Morland J. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. *Annals of Epidemiology* 2007;**17**(8):597-602.
101. Epstein RH, Gratch DM, Grunwald Z. Development of a scheduled drug diversion surveillance system based on an analysis of atypical drug transactions. *Anesthesia & Analgesia* 2007;**105**(4):1053-60, table of contents.
102. Epstein RH, Gratch DM, McNulty S, Grunwald Z. Validation of a system to detect scheduled drug diversion by anesthesia care providers. *Anesthesia & Analgesia* 2011;**113**(1):160-4.
103. Facklam DP, Baker MI, Gardner JS, Herbert C, Grava-Gubins I. Is post-marketing drug surveillance possible in the family practice setting? A collaborative study. *Canadian Family Physician* 1988;**34**:819-22.
104. Fincke BG, Snyder K, Cantillon C, Gaehde S, Standing P, Fiore L, Brophy M, Gagnon DR. Three complementary definitions of polypharmacy: methods, application and comparison of findings in a large prescription database. *Pharmacoepidemiology & Drug Safety* 2005;**14**(2):121-8.
105. Fischer B, Nakamura N, Rush B, Rehm J, Urbanoski K. Changes in and characteristics of admissions to treatment related to problematic prescription opioid use in Ontario, 2004-2009. *Drug & Alcohol Dependence* 2010;**109**(1-3):257-60.
106. Franklin GM, Mai J, Turner J, Sullivan M, Wickizer T, Fulton-Kehoe D. Bending the prescription opioid dosing and mortality curves: impact of the Washington State opioid dosing guideline. *American Journal of Industrial Medicine* 2012;**55**(4):325-31.
107. Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing

- trends and mortality in Washington state workers' compensation, 1996-2002. *American Journal of Industrial Medicine* 2005;**48**(2):91-99.
108. Frauger E, Pauly V, Pradel V, Rouby F, Arditti J, Thirion X, Lapeyre Mestre M, Micallef J. Evidence of clonazepam abuse liability: results of the tools developed by the French Centers for Evaluation and Information on Pharmacodependence (CEIP) network. *Fundamental & Clinical Pharmacology* 2011;**25**(5):633-41.
  109. Frauger E, Pradel V, Natali F, Thirion X, Reggio P, Micallef J. [Misuse of clonazepam (Rivotril): recent trends]. *Therapie* 2006;**61**(1):49-55.
  110. Frauger E, Thirion X, Chanut C, Natali F, Debruyne D, Saillard C, Pradel V, Reggio P, Micallef J. [Misuse of trihexyphenidyl (Artane, Parkinane): recent trends]. *Therapie* 2003;**58**(6):541-7.
  111. Fredheim OM, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway. *European Journal of Pain* 2010;**14**(3):289-94.
  112. Frischer M, Norwood J, Heatlie H, Millson D, Lowdell J, Hickman M, Chapman S, Bashford J. A comparison of trends in problematic drug misuse from two reporting systems. *Journal of Public Health Medicine* 2000;**22**(3):362-7.
  113. Frisher M, Martino O, Crome I, Croft P. Trends in drug misuse recorded in primary care in the UK from 1998 to 2005. *Journal of Public Health* 2009;**31**(1):69-73.
  114. Gahr M, Freudenmann RW, Hiemke C, Kolle MA, Schonfeldt-Lecuona C. Pregabalin abuse and dependence in Germany: results from a database query. *European Journal of Clinical Pharmacology* 2013;**69**(6):1335-42.
  115. Gemmell I, Millar T, Hay G. Capture-recapture estimates of problem drug use and the use of simulation based confidence intervals in a stratified analysis. *Journal of Epidemiology and Community Health* 2004;**58**(9):758-765.
  116. Gerson LW, Boex J, Hua K, Liebelt RA, Zumbar WR, Bush D, Givens C. Medical care use by treated and untreated substance abusing Medicaid patients. *Journal of Substance Abuse Treatment* 2001;**20**(2):115-20.
  117. Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug & Alcohol Review* 2007;**26**(4):405-10.
  118. Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997-2002. *Journal of Pain & Symptom Management* 2004;**28**(2):176-88.
  119. Gokhale M, Martin BC. Prescription-acquired acetaminophen use and potential overuse patterns: 2001-2008. *Pharmacoepidemiology & Drug Safety* 2012;**21**(2):226-30.
  120. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Archives of Internal Medicine* 2011;**171**(7):686-91.
  121. Gomes T, Paterson JM, Juurlink DN, Dhalla IA, Mamdani MM. Reformulation of controlled-release oxycodone and pharmacy dispensing patterns near the US-Canada border. *Open Medicine: A Peer-reviewed, Independent, Open-access Journal* 2012;**6**(4):e141-5.
  122. Grann M, Fazel S. Substance misuse and violent crime: Swedish population study. *BMJ* 2004;**328**(7450):1233-4.
  123. Green TC, Mann MR, Bowman SE, Zaller N, Soto X, Gadea J, Cordy C, Kelly P,

- Friedmann PD. How does use of a prescription monitoring program change medical practice? *Pain Medicine* 2012;**13**(10):1314-23.
124. Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Morland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Med* 2008;**9**(8):818-22.
  125. Han H, Kass PH, Wilsey BL, Li CS. Age, gender, and earlier opioid requirement associations with the rate of dose escalation in long-term opioid therapy. *Journal of Opioid Management* 2013;**9**(2):129-138.
  126. Hartung DM, Middleton L, Haxby DG, Koder M, Ketchum KL, Chou R. Rates of adverse events of long-acting opioids in a state Medicaid program. *Annals of Pharmacotherapy* 2007;**41**(6):921-928.
  127. Haukka J, Arffman M, Partonen T, Sihvo S, Elovainio M, Tiihonen J, Lonnqvist J, Keskimaki I. Antidepressant use and mortality in Finland: a register-linkage study from a nationwide cohort. *European Journal of Clinical Pharmacology* 2009;**65**(7):715-20.
  128. Havens JR, Stoops WW, Leukefeld CG, Garrity TF, Carlson RG, Falck R, Wang J, Booth BM. Prescription opiate misuse among rural stimulant users in a multistate community-based study. *American Journal of Drug & Alcohol Abuse* 2009;**35**(1):18-23.
  129. Havens JR, Talbert JC, Walker R, Leedham C, Leukefeld CG. Trends in controlled-release oxycodone (OxyContin) prescribing among Medicaid recipients in Kentucky, 1998-2002. *Journal of Rural Health* 2006;**22**(3):276-8.
  130. Hay G. Capture-recapture estimates of drug misuse in urban and non-urban settings in the north east of Scotland. *Addiction* 2000;**95**(12):1795-803.
  131. Hay G, Gannon M. Capture-recapture estimates of the local and national prevalence of problem drug use in Scotland. *International Journal of Drug Policy* 2006;**17**(3):203-210.
  132. Heaton PC, Cluxton RJ, Jr., Moomaw CJ. Acetaminophen overuse in the Ohio Medicaid population. *Journal of American Pharmacy Association (2003)* 2003;**43**(6):680-4.
  133. Heilbronn C, Lloyd B, McElwee P, Eade A, Lubman DI. Trends in quetiapine use and non-fatal quetiapine-related ambulance attendances. *Drug & Alcohol Review* 2013;**32**(4):405-11.
  134. Holman JE, Stoddard GJ, Higgins TF. Rates of prescription opiate use before and after injury in patients with orthopaedic trauma and the risk factors for prolonged opiate use. *Journal of Bone & Joint Surgery - American Volume* 2013;**95**(12):1075-80.
  135. Hsu MH, Yeh YT, Chen CY, Liu CH, Liu CT. Online detection of potential duplicate medications and changes of physician behavior for outpatients visiting multiple hospitals using national health insurance smart cards in Taiwan. *International Journal of Medical Informatics* 2011;**80**(3):181-189.
  136. Hsu YC, Huang WF, Cheng SH. Inappropriate prescribing of non-narcotic analgesics in Taiwan's NHI ambulatory visits. *Chinese Pharmaceutical Journal* 2004;**56**(3-6):111-120.
  137. Huang WF, Lai IC. Potentially inappropriate prescribing for insomnia in elderly outpatients in Taiwan. *International Journal of Clinical Pharmacology & Therapeutics* 2006;**44**(7):335-42.
  138. Ineke Neutel C, Skurtveit S, Berg C. Polypharmacy of potentially addictive medication

- in the older persons--quantifying usage. *Pharmacoepidemiology & Drug Safety* 2012;**21**(2):199-206.
139. Jorgensen VRK. An approach to reduce benzodiazepine and cyclopyrrolone use in general practice : a study based on a Danish population. *CNS Drugs* 2007;**21**(11):947-55.
  140. Kelly BC, Parsons JT. Prescription drug misuse and sexual risk taking among HIV-negative MSM. *AIDS & Behavior* 2013;**17**(3):926-30.
  141. Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Within-family environmental transmission of drug abuse: a Swedish national study. *JAMA Psychiatry* 2013;**70**(2):235-42.
  142. Kendler KS, Sundquist K, Ohlsson H, Palmer K, Maes H, Winkleby MA, Sundquist J. Genetic and familial environmental influences on the risk for drug abuse: a national Swedish adoption study. *Archives of General Psychiatry* 2012;**69**(7):690-7.
  143. Kjosavik SR, Ruths S, Hunskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *European Journal of Clinical Pharmacology* 2012;**68**(3):311-9.
  144. Knisely JS, Campbell ED, Dawson KS, Schnoll SH. Tramadol post-marketing surveillance in health care professionals. *Drug & Alcohol Dependence* 2002;**68**(1):15-22.
  145. Kobus AM, Smith DH, Morasco BJ, Johnson ES, Yang X, Petrik AF, Deyo RA. Correlates of higher-dose opioid medication use for low back pain in primary care. *Journal of Pain* 2012;**13**(11):1131-1138.
  146. Koeppe J, Lichtenstein K, Armon C, Chmiel JS, Buchacz K, Wood K, Brooks JT. Factors associated with initiation of prolonged analgesic use among patients in the HIV outpatient study (HOPS). *Clinical Journal of Pain* 2011;**27**(8):699-706.
  147. Krigsman K, Melander A, Carlsten A, Ekedahl A, Nilsson JL. Refill non-adherence to repeat prescriptions leads to treatment gaps or to high extra costs. *Pharmacy World & Science* 2007;**29**(1):19-24.
  148. Kunz D, Bineau S, Maman K, Milea D, Toumi M. Benzodiazepine discontinuation with prolonged-release melatonin: Hints from a German longitudinal prescription database. *Expert Opinion on Pharmacotherapy* 2012;**13**(1):9-16.
  149. Kurdyak P, Gomes T, Yao Z, Mamdani MM, Hellings C, Fischer B, Rehm J, Bayoumi AM, Juurlink DN. Use of other opioids during methadone therapy: a population-based study. *Addiction* 2012;**107**(4):776-780.
  150. LaFleur J, McBeth C, Gunning K, Oderda L, Steinvoort C, Oderda GM. Prevalence of drug-related problems and cost-savings opportunities in medicaid high utilizers identified by a pharmacist-run drug regimen review center. *Journal of Managed Care Pharmacy* 2006;**12**(8):677-85.
  151. Leider HL, Dhaliwal J, Davis EJ, Kulakodlu M, Buikema AR. Healthcare costs and nonadherence among chronic opioid users. *American Journal of Managed Care* 2011;**17**(1):32-40.
  152. Li JS, Zhang XG, Wang HQ, Wang Y, Wang JM, Shao QD. The meaningful use of EMR in chinese hospitals: A case study on curbing antibiotic abuse. *Journal of Medical Systems* 2013;**37**(2).
  153. Log T, Hartz I, Handal M, Tverdal A, Furu K, Skurtveit S. The association between smoking and subsequent repeated use of prescribed opioids among adolescents and young adults-a population-based cohort study. *Pharmacoepidemiology & Drug*

- Safety* 2011;**20**(1):90-8.
154. Log T, Skurtveit S, Selmer R, Tverdal A, Furu K, Hartz I. The association between prescribed opioid use for mothers and children: a record-linkage study. *European Journal of Clinical Pharmacology* 2013;**69**(1):111-8.
  155. Lund IO, Skurtveit S, Engeland A, Furu K, Ravndal E, Handal M. Prescription drug use among pregnant women in opioid Maintenance Treatment. *Addiction* 2013;**108**(2):367-76.
  156. MacFadyen L, Eadie D, McGowan T. Community pharmacists' experience of over-the-counter medicine misuse in Scotland. *Journal of The Royal Society for the Promotion of Health* 2001;**121**(3):185-192.
  157. Manchikanti L, Fellows B, Damron KS, Pampati V, McManus CD. Prevalence of illicit drug use among individuals with chronic pain in the Commonwealth of Kentucky: an evaluation of patterns and trends. *Journal of the Kentucky Medical Association* 2005;**103**(2):55-62.
  158. Manchikanti L, Manchukonda R, Damron KS, Brandon D, McManus CD, Cash K. Does adherence monitoring reduce controlled substance abuse in chronic pain patients? *Pain Physician* 2006;**9**(1):57-60.
  159. Manchikanti L, Pampati V, Damron KS, Beyer CD, Barnhill RC, Fellows B. Prevalence of prescription drug abuse and dependency in patients with chronic pain in western Kentucky. *Journal of the Kentucky Medical Association* 2003;**101**(11):511-7.
  160. Mark TL, Dilonardo J, Vandivort R, Miller K. Psychiatric and medical comorbidities, associated pain, and health care utilization of patients prescribed buprenorphine. *Journal of Substance Abuse Treatment* 2013;**44**(5):481-487.
  161. Martyres RF, Clode D, Burns JM. Seeking drugs or seeking help? Escalating "doctor shopping" by young heroin users before fatal overdose. *Medical Journal of Australia* 2004;**180**(5):211-4.
  162. McAdam-Marx C, Roland CL, Cleveland J, Oderda GM. Costs of opioid abuse and misuse determined from a Medicaid database. *Journal of Pain & Palliative Care Pharmacotherapy* 2010;**24**(1):5-18.
  163. McCarty D, Argeriou M. The Iowa Managed Substance Abuse Care Plan: access, utilization, and expenditures for Medicaid recipients. *Journal of Behavioral Health Services & Research* 2003;**30**(1):18-25.
  164. McCarty D, Perrin NA, Green CA, Polen MR, Leo MC, Lynch F. Methadone maintenance and the cost and utilization of health care among individuals dependent on opioids in a commercial health plan. *Drug & Alcohol Dependence* 2010;**111**(3):235-40.
  165. McDonald DC, Carlson K, Izrael D. Geographic variation in opioid prescribing in the U.S. *Journal of Pain* 2012;**13**(10):988-96.
  166. McNeely J, Gourevitch MN, Paone D, Shah S, Wright S, Heller D. Estimating the prevalence of illicit opioid use in New York City using multiple data sources. *BMC Public Health* 2012;**12**:443.
  167. Mellbye A, Svendsen K, Borchgrevink PC, Skurtveit S, Fredheim OMS. Concomitant medication among persistent opioid users with chronic non-malignant pain. *Acta Anaesthesiologica Scandinavica* 2012;**56**(10):1267-76.
  168. Michielsen P, De Schepper P. Trends of analgesic nephropathy in two high-endemic regions with different legislation. *Journal of the American Society of Nephrology* 2001;**12**(3):550-556.

169. Miller NS, Greenfeld A. Patient characteristics and risks factors for development of dependence on hydrocodone and oxycodone. *American Journal of Therapeutics* 2004;**11**(1):26-32.
170. Miller TR, Lestina DC, Smith GS. Injury risk among medically identified alcohol and drug abusers. *Alcoholism: Clinical & Experimental Research* 2001;**25**(1):54-9.
171. Morasco BJ, Duckart JP, Carr TP, Deyo RA, Dobscha SK. Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. *Pain* 2010;**151**(3):625-32.
172. Morgan L, Weaver M, Sayeed Z, Orr R. The use of prescription monitoring programs to reduce opioid diversion and improve patient safety. *Journal of Pain and Palliative Care Pharmacotherapy* 2013;**27**(1):4-9.
173. Morrato EH, Dodd S, Oderda G, Haxby DG, Allen R, Valuck RJ. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid Population, 1998-2003. *Clinical Therapeutics* 2007;**29**(1):183-195.
174. Mort JR, Shiyabola OO, Ndehi LN, Xu Y, Stacy JN. Opioid-paracetamol prescription patterns and liver dysfunction: a retrospective cohort study in a population served by a US health benefits organization. *Drug Safety* 2011;**34**(11):1079-88.
175. Nicholas R, Roche A, Dobbin M, Lee N. Beyond the paper trail: Using technology to reduce escalating harms from opioid prescribing in Australia. *Australian and New Zealand Journal of Public Health* 2013;**37**(2):139-147.
176. Nordbo A, Skurtveit S, Borchgrevink PC, Kaasa S, Fredheim OM. Low-dose transdermal buprenorphine - long-term use and co-medication with other potentially addictive drugs. *Acta Anaesthesiologica Scandinavica* 2012;**56**(1):88-94.
177. Novack V, Jotkowitz AB, Delgado J, Shleyfer E, Barski L, Porath A. Deliberate self-poisoning with acetaminophen: a comparison with other medications. *European Journal of Internal Medicine* 2005;**16**(8):585-9.
178. Oliva EM, Harris AHS, Trafton JA, Gordon AJ. Receipt of opioid agonist treatment in the Veterans Health Administration: Facility and patient factors. *Drug and Alcohol Dependence* 2012;**122**(3):241-246.
179. Orriols L, Philip P, Moore N, Castot A, Gadegbeku B, Delorme B, Mallaret M, Lagarde E, Group CR. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. *Clinical Pharmacology & Therapeutics* 2011;**89**(4):595-601.
180. Otoom S, Culligan K, Al-Assoomi B, Al-Ansari T. Analysis of drug prescriptions in primary health care centres in Bahrain. *Eastern Mediterranean Health Journal* 2010;**16**(5):511-5.
181. Owens C, Pugmire B, Salness T, Culbertson V, Force R, Cady P, Steiner J. Abuse potential of carisoprodol: a retrospective Review of Idaho Medicaid pharmacy and medical claims data. *Clinical Therapeutics* 2007;**29**(10):2222-2225.
182. Painter JT, Crofford LJ, Talbert J. Geographic variation of chronic opioid use in fibromyalgia. *Clinical Therapeutics* 2013;**35**(3):303-311.
183. Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. *Pain Medicine* 2011;**12**(5):747-54.
184. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, Landen MG, Harvey W, Loring LD. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Medicine* 2012;**13**(1):87-95.
185. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West

- Virginia. *Addiction* 2009;**104**(9):1541-8.
186. Pavone E, Banfi R, Vaiani M, Panconesi A. Patterns of triptans use: a study based on the records of a community pharmaceutical department. *Cephalalgia* 2007;**27**(9):1000-4.
  187. Pesa J, Meyer R, Quock TP, Rattana SK, Mody SH, Wander C. Opioid utilization patterns among Medicare patients with diabetic peripheral neuropathy. *American Health and Drug Benefits* 2013;**6**(3).
  188. Petitjean S, Ladewig D, Meier CR, Amrein R, Wiesbeck GA. Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies. *International Clinical Psychopharmacology* 2007;**22**(5):292-8.
  189. Pimlott NJG, Hux JE, Wilson LM, Kahan M, Li C, Rosser WW. Educating physicians to reduce benzodiazepine use by elderly patients: a randomized controlled trial. *CMAJ Canadian Medical Association Journal* 2003;**168**(7):835-9.
  190. Pottegard A, Hallas J. Physicians' and pharmacies' overview of patients' medication. An analysis of fidelity coefficients.[Erratum appears in Eur J Clin Pharmacol. 2012 Jan;68(1):107]. *European Journal of Clinical Pharmacology* 2011;**67**(9):919-24.
  191. Preville M, Bosse C, Vasiliadis H-M, Voyer P, Laurier C, Berbiche D, Perodeau G, Grenier S, Beland S-G, Dionne P-A, Gentil L, Moride Y. Correlates of potentially inappropriate prescriptions of benzodiazepines among older adults: results from the ESA study. *Canadian Journal on Aging* 2012;**31**(3):313-22.
  192. Prince JD, Akincigil A, Hoover DR, Walkup JT, Bilder S, Crystal S. Substance abuse and hospitalization for mood disorder among Medicaid beneficiaries. *American Journal of Public Health* 2009;**99**(1):160-7.
  193. Ravera S, van Rein N, de Gier JJ, de Jong-van den Berg LTW. Road traffic accidents and psychotropic medication use in The Netherlands: a case-control study. *British Journal of Clinical Pharmacology* 2011;**72**(3):505-13.
  194. Ray WA, Murray KT, Kawai V, Graham DJ, Cooper WO, Hall K, Michael Stein C. Propoxyphene and the risk of out-of-hospital death. *Pharmacoepidemiology and Drug Safety* 2013;**22**(4):403-412.
  195. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med* 2002;**17**(3):173-9.
  196. Reifler LM, Droz D, Bailey JE, Schnoll SH, Fant R, Dart RC, Bucher Bartelson B. Do prescription monitoring programs impact state trends in opioid abuse/misuse? *Pain Medicine* 2012;**13**(3):434-42.
  197. Rhee Y, Taitel MS, Walker DR, Lau DT. Narcotic drug use among patients with lower back pain in employer health plans: a retrospective analysis of risk factors and health care services. *Clinical Therapeutics* 2007;**29 Suppl**:2603-12.
  198. Roland CL, Joshi AV, Mardekian J, Walden SC, Harnett J. Prevalence and cost of diagnosed opioid abuse in a privately insured population in the United States. *Journal of Opioid Management* 2013;**9**(3):161-75.
  199. Rouve N, Bagheri H, Telmon N, Pathak A, Franchitto N, Schmitt L, Rouge D, Lapeyre-Mestre M, Montastruc J-L, French Association of Regional Pharmacovigilance C. Prescribed drugs and violence: a case/noncase study in the French Pharmacovigilance Database. *European Journal of Clinical Pharmacology* 2011;**67**(11):1189-98.

200. Roux P, Carrieri PM, Cohen J, Ravoux I, Spire B, Gossop M, Comer SD. Non-medical use of opioids among HIV-infected opioid dependent individuals on opioid maintenance treatment: the need for a more comprehensive approach. *Harm Reduction Journal* 2011;**8**:31.
201. Sambamoorthi U, Warner LA, Crystal S, Walkup J. Drug abuse, methadone treatment, and health services use among injection drug users with AIDS. *Drug and Alcohol Dependence* 2000;**60**(1):77-89.
202. Schuman-Olivier Z, Albanese M, Nelson SE, Roland L, Puopolo F, Klinker L, Shaffer HJ. Self-treatment: illicit buprenorphine use by opioid-dependent treatment seekers. *Journal of Substance Abuse & Treatment* 2010;**39**(1):41-50.
203. Sears JM, Krupski A, Joesch JM, Estee SL, He L, Shah MF, Huber A, Dunn C, Ries R, Roy-Byrne PP. The use of administrative data as a substitute for individual screening scores in observational studies related to problematic alcohol or drug use. *Drug & Alcohol Dependence* 2010;**111**(1-2):89-96.
204. Shen WW, Chang C, Hsieh WC, Yeh CJ, Chiu FY, Chuang YC. The flunitrazepam abuse prevention program at a general hospital in Taiwan: A descriptive study. *Psychiatry and Clinical Neurosciences* 2002;**56**(4):425-430.
205. Silverberg MJ, Ray GT, Saunders K, Rutter CM, Campbell CI, Merrill JO, Sullivan MD, Banta-Green CJ, Von Korff M, Weisner C. Prescription long-term opioid use in HIV-infected patients. *Clinical Journal of Pain* 2012;**28**(1):39-46.
206. Simoni-Wastila L, Tompkins C. Balancing diversion control and medical necessity: the case of prescription drugs with abuse potential. *Substance Use & Misuse* 2001;**36**(9-10):1275-96.
207. Skurtveit S, Furu K, Bramness J, Selmer R, Tverdal A. Benzodiazepines predict use of opioids--a follow-up study of 17,074 men and women. *Pain Medicine* 2010;**11**(6):805-14.
208. Skurtveit S, Furu K, Kaasa S, Borchgrevink PC. Introduction of low dose transdermal buprenorphine -- did it influence use of potentially addictive drugs in chronic non-malignant pain patients? *European Journal of Pain* 2009;**13**(9):949-53.
209. Skurtveit S, Furu K, Selmer R, Handal M, Tverdal A. Nicotine dependence predicts repeated use of prescribed opioids. Prospective population-based cohort study. *Annals of Epidemiology* 2010;**20**(12):890-7.
210. Smith RC, Frank C, Gardiner JC, Lamerato L, Rost KM. Pilot study of a preliminary criterion standard for prescription opioid misuse. *American Journal on Addictions* 2010;**19**(6):523-8.
211. Stene LE, Dyb G, Tverdal A, Jacobsen GW, Schei B. Intimate partner violence and prescription of potentially addictive drugs: prospective cohort study of women in the Oslo Health Study. *BMJ Open* 2012;**2**(2):e000614.
212. Suokas JT, Suvisaari JM, Haukka J, Korhonen P, Tiihonen J. Description of long-term polypharmacy among schizophrenia outpatients. *Social Psychiatry & Psychiatric Epidemiology* 2013;**48**(4):631-8.
213. Svendsen K, Skurtveit S, Romundstad P, Borchgrevink PC, Fredheim OM. Differential patterns of opioid use: defining persistent opioid use in a prescription database. *European Journal of Pain* 2012;**16**(3):359-69.
214. Swedlow A, Ireland J, Johnson G. Prescribing patterns of schedule II opioids in California workers' compensation. 2011.
215. Tholen K, Hoffmann F. High use of tramadol in Germany: An analysis of statutory

- health insurance data. *Pharmacoepidemiology and Drug Safety* 2012;**21**(9):1013-1021.
216. Trescott CE, Beck RM, Seelig MD, Von Korff MR. Group Health's initiative to avert opioid misuse and overdose among patients with chronic noncancer pain. *Health Affairs (Millwood)* 2011;**30**(8):1420-4.
217. Tyrfingsson T, Thorgeirsson TE, Geller F, Runarsdottir V, Hansdottir I, Bjornsdottir G, Wiste AK, Jonsdottir GA, Stefansson H, Gulcher JR, Oskarsson H, Gudbjartsson D, Stefansson K. Addictions and their familiarity in Iceland. *Annals of the New York Academy of Sciences* 2010;**1187**:208-17.
218. van Eijk JTM, Bosma H, Jonkers CCM, Lamers F, Muijters PEM. Prescribing antidepressants and benzodiazepines in the Netherlands: is chronic physical illness involved? *Depression Research and Treatment* 2010;**2010**:105931.
219. van Hulten R, Isacson D, Bakker A, Leufkens HG. Comparing patterns of long-term benzodiazepine use between a Dutch and a Swedish community. *Pharmacoepidemiology & Drug Safety* 2003;**12**(1):49-53.
220. VanHaaren AM, Lapane KL, Hughes CM. Effect of triplicate prescription policy on benzodiazepine administration in nursing home residents. *Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy* 2001;**21**(10):1159-66.
221. Vedsted P, Sorensen HT, Mortensen JT. Drug prescription for adult frequent attenders in Danish general practice: a population-based study. *Pharmacoepidemiology & Drug Safety* 2004;**13**(10):717-24.
222. Victorri-Vigneau C, Larour K, Simon D, Pivette J, Jolliet P. Creating and validating a tool able to detect fraud by prescription falsification from health insurance administration databases. *Therapie* 2009;**64**(1):27-31.
223. Viola R, Csukonyi K, Doro P, Janka Z, Soos G. Reasons for polypharmacy among psychiatric patients. *Pharmacy World & Science* 2004;**26**(3):143-7.
224. Wagner AK, Soumerai SB, Zhang F, Mah C, Simoni-Wastila L, Cosler L, Fanning T, Gallagher P, Ross-Degnan D. Effects of state surveillance on new post-hospitalization benzodiazepine use. *International Journal for Quality in Health Care* 2003;**15**(5):423-431.
225. White AG, Birnbaum HG, Mareva MN, Daher M, Vallow S, Schein J, Katz N. Direct costs of opioid abuse in an insured population in the United States. *Journal of Managed Care Pharmacy: JMCP* 2005;**11**(6):469-479.
226. White AG, Birnbaum HG, Rothman DB, Katz N. Development of a budget-impact model to quantify potential cost savings from prescription opioids designed to deter abuse or ease of extraction. *Applied Health Economics & Health Policy* 2009;**7**(1):61-70.
227. Winther RB, Bramness JG. [Prescription shopping of addictive drugs in Norway]. *Tidsskr Nor Laegeforen* 2009;**129**(6):517-20.
228. Wu C-S, Wang S-C, Chang IS, Lin K-M. The association between dementia and long-term use of benzodiazepine in the elderly: nested case-control study using claims data. *American Journal of Geriatric Psychiatry* 2009;**17**(7):614-20.
229. Zarowitz BJ, Stebelsky LA, Muma BK, Romain TM, Peterson EL. Reduction of high-risk polypharmacy drug combinations in patients in a managed care setting. *Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy* 2005;**25**(11):1636-45.

## Supplementary Material 2.6. Reference List of Included Studies (N=52)<sup>a</sup>

1. Bachs LC, Bramness JG, Engeland A, Skurtveit S. Repeated dispensing of codeine is associated with high consumption of benzodiazepines. *Nor Epidemiol.* 2008;18(2):185-190.
2. Bellanger L, Vigneau C, Pivette J, Jolliet P, Sébille V. Discrimination of psychotropic drugs over-consumers using a threshold exceedance based approach. *Stat Anal Data Min.* 2013;6(2):91-101.
3. Bramness JG, Furu K, Engeland A, Skurtveit S. Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol.* 2007;64(2):210-218.
4. Bramness JG, Rossow I. Can the total consumption of a medicinal drug be used as an indicator of excessive use? The case of carisoprodol. *Drugs: Education, Prevention and Policy.* 2010;17(2):168-180.
5. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Assessing opioid shopping behaviour: a large cohort study from a medication dispensing database in the US. *Drug Saf.* 2012;35(4):325-334.
6. Cepeda MS, Fife D, Berlin JA, Mastrogiovanni G, Yuan Y. Characteristics of prescribers whose patients shop for opioids: results from a cohort study. *J Opioid Manag.* 2012;8(5):285-291.
7. Cepeda MS, Fife D, Chow W, Mastrogiovanni G, Henderson SC. Opioid shopping behavior: how often, how soon, which drugs, and what payment method. *J Clin Pharmacol.* 2013;53(1):112-117.
8. Cepeda MS, Fife D, Vo L, Mastrogiovanni G, Yuan Y. Comparison of opioid doctor shopping for tapentadol and oxycodone: a cohort study. *J Pain.* 2013;14(2):158-164.
9. Cepeda MS, Fife D, Yuan Y, Mastrogiovanni G. Distance traveled and frequency of interstate opioid dispensing in opioid shoppers and nonshoppers. *J Pain.* 2013;14(10):1158-1161.
10. Dormuth CR, Miller TA, Huang A, et al. Effect of a centralized prescription network on inappropriate prescriptions for opioid analgesics and benzodiazepines. *CMAJ.* 2012;184(16):E852-856.
11. Feroni I, Peretti-Watel P, Paraponaris A, et al. French general practitioners' attitudes and prescription patterns toward buprenorphine maintenance treatment: does doctor shopping reflect buprenorphine misuse? *J Addict Dis.* 2005;24(3):7-22.
12. Frauger E, Pauly V, Thirion X, et al. Estimation of clonazepam abuse liability: a new method using a reimbursed drug database. *Int Clin Psychopharmacol.* 2009;24(6):318-324.
13. Frauger E, Pauly V, Natali F, et al. Patterns of methylphenidate use and assessment of its abuse and diversion in two French administrative areas using a proxy of deviant behaviour determined from a reimbursement database: main trends from 2005 to 2008. *CNS Drugs.* 2011;25(5):415-424.
14. Fredheim OMS, Skurtveit S, Moroz A, Breivik H, Borchgrevink PC. Prescription pattern of codeine for non-malignant pain: a pharmacoepidemiological study from the Norwegian Prescription Database. *Acta Anaesthesiol Scand.* 2009;53(5):627-633.
15. Gilson AM, Fishman SM, Wilsey BL, Casamalhuapa C, Baxi H. Time series analysis of California's prescription monitoring program: impact on prescribing and multiple provider episodes. *J Pain.* 2012;13(2):103-111.

16. Gjerden P, Bramness JG, Slørdal L. The use and potential abuse of anticholinergic antiparkinson drugs in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol*. 2009;67(2):228-233.
17. Goodman FDC, Glassman P. Evaluating potentially aberrant outpatient prescriptions for extended-release oxycodone. *Am J Health-Syst Pharm*. 2005;62(24):2604-2608.
18. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008;300(22):2613-2620.
19. Han H, Kass PH, Wilsey BL, Li C-S. Individual and county-level factors associated with use of multiple prescribers and multiple pharmacies to obtain opioid prescriptions in California. *PLoS ONE*. 2012;7(9):e46246.
20. Hartz I, Tverdal A, Skurtveit S. Social inequalities in use of potentially addictive drugs in Norway - use among disability pensioners. *Nor Epidemiol*. 2009;19(2):209-218.
21. Hoffman L, Enders JL, Pippins J, Segal R. Reducing claims for prescription drugs with a high potential for abuse. *Am J Health-Syst Pharm*. 2003;60(4):371-374.
22. Katz N, Panas L, Kim M, et al. Usefulness of prescription monitoring programs for surveillance - analysis of Schedule II opioid prescription data in Massachusetts, 1996-2006. *Pharmacoepidemiol Drug Saf*. 2010;19(2):115-123.
23. Logan J, Liu Y, Paulozzi L, Zhang K, Jones C. Opioid prescribing in emergency departments: the prevalence of potentially inappropriate prescribing and misuse. *Med Care*. 2013;51(8):646-653.
24. Mailloux AT, Cummings SW, Mugdh M. A decision support tool for identifying abuse of controlled substances by ForwardHealth Medicaid members. *J Hosp Mark Public Relations*. 2010;20(1):34-55.
25. Martin BC, Fan M-Y, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med*. 2011;26(12):1450-1457.
26. McDonald DC, Carlson KE. Estimating the prevalence of opioid diversion by "doctor shoppers" in the United States. *PLoS ONE*. 2013;8(7):e69241.
27. Nordmann S, Pradel V, Lapeyre-Mestre M, et al. Doctor shopping reveals geographical variations in opioid abuse. *Pain Physician*. 2013;16(1):89-100.
28. Parente ST, Kim SS, Finch MD, et al. Identifying controlled substance patterns of utilization requiring evaluation using administrative claims data. *Am J Manag Care*. 2004;10(11 Pt1):783-790.
29. Pauly V, Frauger E, Pradel V, et al. Which indicators can public health authorities use to monitor prescription drug abuse and evaluate the impact of regulatory measures? Controlling high dosage buprenorphine abuse. *Drug Alcohol Depend*. 2011;113(1):29-36.
30. Pauly V, Frauger E, Pradel V, et al. Monitoring of benzodiazepine diversion using a multi-indicator approach. *Int Clin Psychopharmacol*. 2011;26(5):268-277.
31. Pauly V, Pradel V, Pourcel L, et al. Estimated magnitude of diversion and abuse of opioids relative to benzodiazepines in France. *Drug Alcohol Depend*. 2012;126(1-2):13-20.
32. Pearson S-A, Soumerai S, Mah C, et al. Racial disparities in access after regulatory surveillance of benzodiazepines. *Arch Intern Med*. 2006;166(5):572-579.
33. Peirce GL, Smith MJ, Abate MA, Halverson J. Doctor and pharmacy shopping for controlled substances. *Med Care*. 2012;50(6):494-500.

34. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, Begaud B. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. *Pharmacoepidemiol Drug Saf.* 2004;13(7):473-481.
35. Pradel V, Frauger E, Thirion X, et al. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. *Pharmacoepidemiol Drug Saf.* 2009;18(1):36-43.
36. Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using 'doctor shopping' as an indicator. *CNS Drugs.* 2010;24(7):611-620.
37. Rice JB, White AG, Birnbaum HG, Schiller M, Brown DA, Roland CL. A model to identify patients at risk for prescription opioid abuse, dependence, and misuse. *Pain Med.* 2012;13(9):1162-1173.
38. Ross-Degnan D, Simoni-Wastila L, Brown JS, et al. A controlled study of the effects of state surveillance on indicators of problematic and non-problematic benzodiazepine use in a Medicaid population. *Int J Psychiatry Med.* 2004;34(2):103-123.
39. Rouby F, Pradel V, Frauger E, et al. Assessment of abuse of tianeptine from a reimbursement database using 'doctor-shopping' as an indicator. *Fundam Clin Pharmacol.* 2012;26(2):286-294.
40. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan.[Erratum appears in JAMA. 2012 Jun 20;307(23):2489]. *JAMA.* 2012;307(9):940-947.
41. Simoni-Wastila L, Ross-Degnan D, Mah C, et al. A retrospective data analysis of the impact of the New York triplicate prescription program on benzodiazepine use in Medicaid patients with chronic psychiatric and neurologic disorders. *Clin Ther.* 2004;26(2):322-336.
42. Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? *Pain.* 2011;152(7):1555-1561.
43. Soumerai SB, Simoni-Wastila L, Singer C, et al. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. *Psychiatr Serv.* 2003;54(7):1006-1011.
44. Sullivan MD, Edlund MJ, Fan M-Y, Devries A, Brennan Braden J, Martin BC. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP Study. *Pain.* 2010;150(2):332-339.
45. Thirion X, Lapierre V, Micallef J, et al. Buprenorphine prescription by general practitioners in a French region. *Drug Alcohol Depend.* 2002;65(2):197-204.
46. Victorri-Vigneau C, Basset G, Jolliet P. How a novel programme for increasing awareness of health professionals resulted in a 14% decrease in patients using excessive doses of psychotropic drugs in western France. *Eur J Clin Pharmacol.* 2006;62(4):311-316.
47. Victorri-Vigneau C, Sebille V, Gerardin M, Simon D, Pivette J, Jolliet P. Epidemiological characterization of drug overconsumption: the example of antidepressants. *J Addict Dis.* 2011;30(4):342-350.

48. Victorri-Vigneau C, Feuillet F, Wainstein L, et al. Pharmacoepidemiological characterisation of zolpidem and zopiclone usage. *Eur J Clin Pharmacol.* 2013;69(11):1965-1972.
49. Wainstein L, Victorri-Vigneau C, Seville V, et al. Pharmacoepidemiological characterization of psychotropic drugs consumption using a latent class analysis. *Int Clin Psychopharmacol.* 2011;26(1):54-62.
50. White AG, Birnbaum HG, Schiller M, Tang J, Katz NP. Analytic models to identify patients at risk for prescription opioid abuse. *Am J Manag Care.* 2009;15(12):897-906.
51. Wilsey BL, Fishman SM, Gilson AM, et al. Profiling multiple provider prescribing of opioids, benzodiazepines, stimulants, and anorectics. *Drug Alcohol Depend.* 2010;112(1-2):99-106.
52. Wilsey BL, Fishman SM, Gilson AM, et al. An analysis of the number of multiple prescribers for opioids utilizing data from the California Prescription Monitoring Program. *Pharmacoepidemiol Drug Saf.* 2011;20(12):1262-1268.

<sup>a</sup>Reference list for Electronic Supplementary Material 7-9

**Supplementary Material 2.7.** Summary of included studies (N=52)<sup>a</sup>

First Author Year of Publication Setting (Observation period) <sup>b</sup>	Aim(s) <sup>c</sup> (Drug class[es] of interest)	Cohort(s) details <sup>c</sup>	Measures of prescription drug misuse with a defined threshold (time period of assessment) <sup>d</sup>	Other findings relevant to prescription drug misuse (time period of assessment)	
Bachs <sup>1</sup> 2008 Norway (2006)	Describe 'high users' concomitant drug use (opioid).	<b>A) Cohort</b> (N=386,836): ≥1 codeine dispensing. Excluded if: cancer patient; incomplete patient identifiers; or, use in hospitals, nursing homes or physician's office.	1) <i>Moderate/high codeine user</i> (≥120 DDD): highest 10% of codeine users (12 months) <b>A) 10.7%</b> (n=41,459) 2) <i>High drug-user</i> : dispensed ≥100 DDD of BZD and/or ≥15 DDD of carisoprodol (12 months) <b>A) 50.1%</b> (n=193,804); 41.9% (n=162,084) dispensed high amount of BZD or carisoprodol; 8.2% (n=31,720) dispensed high amounts of BZD and carisoprodol.	*Moderate/high codeine use and concurrent high use of BZD (≥100 DDD) or carisoprodol (≥15 DDD) by sex: Female: 6.9%-8.1% Male: 4.0%-5.7% *From 10 years of age, females had higher rates of codeine utilisation than males.	*In other codeine users (<120 DDD in 12 months): 9.6% received high amounts of BZD (≥100 DDD), carisoprodol (≥15 DDD) or both. *8% of Norwegian population was dispensed a codeine analgesic in 2006.
Bellanger <sup>2</sup> 2013 France (Jul-Dec 2005)	Identify users as over- or normal-drug- users and identify characteristic s associated with overconsump tion (AD and	<b>A) Tianeptine</b> (N=7,263): ≥2 tianeptine dispensings. <b>B) Zolpidem</b> (N=33,584): ≥2 zolpidem dispensings.	1) <i>Doctor shopper</i> : ≥4 prescribers (6 months) <b>A) 0.4%</b> (n=32) <b>B) 0.9%</b> (n=300) 2) <i>Pharmacy shopper</i> : ≥4 dispensing pharmacies (6 months) <b>A) 1.1%</b> (n=78) <b>B) 1.3%</b> (n=438) 3) <i>Excessive user</i> : excessive use threshold derived from Peaks Over	*Overconsumption risk factors for tianeptine and zolpidem: younger age, pharmacy shopping behaviour, consumption of ≥1 anxiolytic drug and R ratio >1 (>1 dispensing per 28 days). *Treatment by a psychiatrist increased the	*Pharmacy shopping increased odds of overconsumption by: 168.5% for tianeptine and 518% for zolpidem users. *The classification rate of POT model: Sensitivity: <b>A) 83%; B) 90%</b>

	Z-drug).		Threshold (POT) model (6 months) Threshold value: proportion (%) of cohort exceeding threshold <b>A) 1.1: 7.2% (n=524)</b> <b>B) 2.0: 0.9% (n=318)</b>	odds of overconsumption for tianeptine by 63%; and for zolpidem decreased the odds of overconsumption by 35.6%.	Specificity: <b>A) 81%; B) 84%</b> Correctly identified: <b>A) 81%; B) 85%</b>
Bramness <sup>3</sup> 2007 Norway (2004)	Explore abuse potential of carisoprodol (other sedative).	<b>A) Cohort</b> (N=83,713): ≥18 years; ≥1 carisoprodol dispensing. Excluded if use in a hospital, nursing home or physician's office; incomplete doctor/user identifiers.	1) <i>Carisoprodol abuser (CA)</i> : ≥2 DDD/day in any prescription (not further specified); dispensed <100 DDD of opioids, and dispensed <100 DDD of BZD (12 months) <b>A) 1.0% (n=815)</b> 2) <i>BZD abuser/anxiety patient (BA)</i> : dispensed ≥100 DDD of BZD and <100 DDD of opioids (12 months) <b>A) 7.8% (n=6,546)</b> 3) <i>Opioid abuser/pain patient (OA)</i> : dispensed ≥100 DDD of opioids (12 months) <b>A) 13.6% (n=11,382)</b> 4) <i>High carisoprodol user</i> : dispensed >15 DDD of carisoprodol (12 months) <b>A) 32.2% (n=26,914)</b> 5) <i>Doctor shopper</i> : ≥4 prescribers (time period not reported) <b>A) 0.5% (n=429)</b> • <i>In user groups defined above, doctor shopper</i> : ≥4 prescribers (time period not reported)	* <i>Number of prescribers</i> (time period not reported) <b>A) 1 prescriber: 88.8% (n=74,305)</b> 2 prescribers: 9.1% (n=7,602) 3 prescribers: 1.6% (n=1,377) ≥4 prescribers: 0.5% (n=429) * <i>Prescribed drug by a high volume prescriber</i> : highest 1% of prescribers in drug volume (12 months) <b>A) 9.4% (n=7,834)</b> CA: 10.8% (n=88) BA: 25.3% (n=1,657) OA: 28.3% (n=3,223) *OAs received 48% of total amount of carisoprodol dispensed in 2004.	*Most carisoprodol was dispensed to users with greater than recommended use who were also dispensed large amounts of BZDs and opioids. *Use of ≥4 prescribers and prescription from a high volume prescriber were more prevalent for drugs with abuse potential, i.e. BZDs and opioids. *High prescribers prescribed 'almost 20%' of drugs with abuse potential, i.e. BZDs and opioids.

			CA: 4.5% (n=37) BA: 1.1% (n=69) OA: 2.0% (n=228)		
Bramness <sup>4</sup> 2010 Norway (2004)	Explore whether total carisoprodol (other sedative) consumption relates to prevalence of excessive carisoprodol use.	<b>A) Cohort</b> (N=84,319): ≥18 years; ≥1 carisoprodol dispensings from a pharmacy. Excluded if dispensed from an institution (not further defined).	<p>1) <i>Excessive carisoprodol user:</i> dispensed &gt;15 DDD of carisoprodol; used &gt;2 times MRDD (time period not specified); ≥2 carisoprodol dispensings; dispensed &lt;100 DDD of BZD, and dispensed &lt;100 DDD of opioids (12 months) <b>A) 1.0%</b> (n=815)</p> <p>2) <i>Highest 1% of carisoprodol users (dispensed ≥480 DDD of carisoprodol)</i> (12 months) <b>A) 1.1%</b> (n=896)</p> <p>3) <i>Extreme carisoprodol user:</i> dispensed &gt;1000 DDD of carisoprodol (12 months) <b>A) 0.2%</b> (n=158)</p> <p>4) <i>Proportion of carisoprodol dispensed to each misuse cohort</i> (12 months) Excessive user: 4.5% Highest 1%: 18.7% Extreme user: 6.1%</p>	<p>*<i>Correlation between misuse cohort and total carisoprodol consumption</i> (12 months) Excessive user: 0.74 Highest 1%: 0.81 Extreme user: 0.61</p> <p>*<i>Correlation between misuse cohort and mean dose</i> (12 months) Excessive user: 0.67 Highest 1%: 0.70 Extreme user: 0.55</p> <p>*An increase in amount of carisoprodol sold resulted in an increase in the number of people identified in the extreme user group.</p>	<p>*<i>Proportion overlap between misuse cohorts</i> (12 months) Excessive user: not reported. Highest 1%: 20% were in extreme group; 7% were excessive users. Extreme user: 4% were excessive users. *45%-64% of variation in prevalence of excessive use was explained by the total sales of carisoprodol.</p>
Cepeda <sup>5</sup> 2012 US (2008 to 18 months after	Compare rates of overlapping opioid prescriptions	<b>Cohort:</b> dispensed ≥1 drug of interest; 3 months of data supplied pre-index prescription;	<p>1) <i>≥1 days of overlapping prescriptions:</i> written by ≥2 prescribers (18 months) <b>A) 13.1%</b> (n=3,297,891) <b>B) 9.8%</b> (n=843,654)</p>	<p>*<i>Median days' drug supply</i> (18 months) <b>A) Opioid:</b> 10 <b>B) BZD:</b> 30 <b>C) Diuretic:</b> 30</p>	

index drug dispensing)	and multiple dispensing pharmacies with BZD (abuse potential) and diuretic ('no abuse potential') users and propose a definition for shopping behaviour that differentiates between drug classes.	dispensing pharmacy(ies) supplied data over entire observation period. <b>A) Opioid</b> (N=25,161,024): dispensed $\geq 1$ opioid. <b>B) BZD</b> (N=8,595,179): dispensed $\geq 1$ BZD. <b>C) Diuretic</b> (N=8,433,456): dispensed $\geq 1$ diuretic.	<b>C) 13.9%</b> (n=1,168,462) • <i>In persons with <math>\geq 1</math> days of overlapping prescriptions: <math>\geq 3</math> prescribers</i> (18 months) Opioid: 5.4% (n=176,731) BZD: 2.5% (n=20,928) Diuretic: 3.2% (n=37,164) • <i>In persons with <math>\geq 1</math> days of overlapping prescriptions: <math>\geq 2</math> dispensing pharmacies</i> (18 months) Opioid: 21.3% (n=700,840) BZD: 17.7% (n=149,036) Diuretic: 8.3% (n=97,004) • <i>In persons with <math>\geq 1</math> days of overlapping prescriptions: <math>\geq 3</math> dispensing pharmacies</i> (18 months) Opioid: 1.3% (n=44,071) BZD: 1.0% (n=8,167) Diuretic: 0.2% (n=2,431) 2) $\geq 4$ days of overlapping prescriptions (18 months) <b>A) 7.7%</b> (n=1,937,130) <b>B) 6.8%</b> (n=587,241) <b>C) 11.1%</b> (n=936,922) 3) $\geq 1$ overlapping prescriptions and $\geq 3$ dispensing pharmacies (18 months) <b>A) 0.2%</b> (n=44,071) <b>B) 0.1%</b> (n=8,167) <b>C) 0.03%</b> (n=2,431)	*Overlapping prescriptions were more common in persons with history of exposure (H) to drug, than naïve users (N). Opioid: 38.3% (H); 8.5% (N) BZD: 19.5% (H); 6.0% (N) Diuretics: 17.5% (H); 10.8% (N). *Opioid cohort: persons aged 25-64 exhibited shopping behaviour ( $\geq 2$ overlapping prescriptions, $\geq 2$ prescribers and $\geq 3$ dispensing pharmacies) more commonly (0.3%) than older users aged $\geq 65$ years (0.1%); prior opioid users exhibited shopping behaviour more commonly (0.8%) than opioid-naïve users (0.1%).	
Cepeda <sup>6</sup> 2012	Report	<b>A) Patients</b>	1) <i>Opioid shopper: <math>\geq 1</math> days</i>	* <u>Prescribers with opioid</u>	* <u>Prescriber</u>

US (2008 to 18 months after index drug dispensing)	prevalence of opioid shopping, heavy opioid shopping behaviour, and prescriber characteristics associated with shopping.	(N=217,851): ≥1 opioid dispensings; 3 months of data pre-index prescription; dispensing pharmacy(ies) supplied data for entire observation period. <b>B) Prescribers</b> (N=858,290): prescribers with ≥1 opioid shopper as a patient.	overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (18 months) <b>A)</b> The extent of drug-users defined as an opioid shopper not reported	<i>shoppers as patients</i> (18 months) <b>B)</b> 13.2% (n=113,034); 86.8% of prescribers had no shoppers as patients. <i>*Prescribers with heavy shoppers (≥5 shopping episodes) as patients</i> (18 months) <b>B)</b> 1.7% (n=14,699); 98.3% of prescribers had no heavy shoppers as patients.	<i>characteristics associated with opioid shoppers:</i> number of patients prescribed an opioid (18-35 users [OR 4.05], 916-1831 [OR 620.13]); male (OR 1.06); aged 70-79 (OR 2.01). <i>*25% of prescribers, prescribed opioids to ≥66 patients, accounting for 82% of shoppers.</i> <i>*Prescriber specialties most associated with opioid shoppers as patients:</i> pain, addiction and emergency drug.
Cepeda <sup>7</sup> 2013 US (2008 to 18 months after index drug dispensing)	Assess prevalence of shopping behaviour in opioid users; how soon shopping behaviour occurs after initial opioid exposure; number of events per	<b>A) Cohort</b> (N=25,161,024): ≥1 opioid dispensings; 3 months of data pre-index prescription; dispensing pharmacy(ies) supplied data over entire observation period.	1) <i>Opioid shopper:</i> ≥1 days overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (18 months) <b>A)</b> 0.3% (n=75,215) of users accounted for 205,932 shopping episodes. • <i>In opioid shoppers, proportion of heavy shoppers:</i> ≥6 shopping episodes (18 months) Opioid shoppers: 9.5% (n=7,157) of users accounted for 44.2% (n=90,997) of shopping episodes	<i>*In opioid shoppers, number of dispensing pharmacies</i> (18 months) 3 pharmacies: 72.7% (n=54,658) 4 pharmacies: 13.9% (n=10,460) 5 pharmacies: 6.8% (n=5,080) 6 pharmacies: 3.2% (n=2,439) ≥7 pharmacies: 3.4% (n=2,578)	*Shoppers (44.9%) more frequently paid in cash than non-shoppers (18.5%). <i>*In shoppers, the most utilised opioids:</i> schedule II and III (32.7%); combination formulation (30.7%); and IR and ER (25.2%) <i>*Median of 234 days to first shopping event</i> <i>*Mean 2.7 shopping</i>

	shopper; preferred opioids; and method of payment.			<p><i>*In opioid shoppers, number of prescribers (18 months)</i></p> <p>2 prescribers: 48.1% (n=36,178)</p> <p>3 prescribers: 31.6% (n=23,790)</p> <p>4 prescribers: 9.3% (n=6,967)</p> <p>5 prescribers: 4.5% (n=3,357)</p> <p>≥6 prescribers: 6.6% (n=4,923)</p>	<p>episodes per shopper</p> <p>*91.7% of subjects with a shopping behaviour were aged 19-64 years.</p> <p>*Prior opioid users were 13.7 times more likely to exhibit shopping behaviour (1.4% vs. 0.1%) than opioid-naïve users.</p>
Cepeda <sup>8</sup> 2013 US (2009 to 12 months after index drug dispensing)	Compare risk of shopping behaviour between tapentadol immediate release (IR) and oxycodone IR (opioid).	<p><b>Cohort:</b> ≥1 tapentadol or oxycodone dispensing; no opioid dispensed in 3 months pre-index prescription.</p> <p>Excluded: dispensed any other opioid 3 days from index date.</p> <p><b>A) Tapentadol IR</b> (N=42,940)</p> <p><b>B) Oxycodone IR</b> (N=112,821)</p> <p>Cohorts were matched 1:4 ratio on month of initial exposure, age,</p>	<p>1) <i>Opioid shopper:</i> ≥1 days overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (12 months)</p> <p><b>A)</b> 0.2% (n=88)</p> <p><b>B)</b> 0.9% (n=967)</p> <p>2) <i>Heavy shopper:</i> ≥5 shopping episodes (12 months)</p> <p><b>A)</b> 0.01% (n=4)</p> <p><b>B)</b> 0.07% (n=80)</p> <p>•<i>In opioid shoppers, proportion of heavy shoppers (12 months)</i></p> <p>Tapentadol: 4.5% (n=4)</p> <p>Oxycodone: 8.3% (n=80)</p>	<p>*Oxycodone users had a higher risk of shopping (3.5 times higher) and heavy shopping behaviour (OR 6.9) than tapentadol users.</p> <p><i>*Mean (SD) shopping episodes per person (12 months)</i></p> <p><b>A)</b> 0.004 (0.1)</p> <p><b>B)</b> 0.02 (0.3)</p> <p><i>*In opioid shoppers, mean (SD) shopping episodes per shopper (12 months)</i></p> <p>Tapentadol: 1.8 (1.9)</p> <p>Oxycodone: 2.1 (2.6)</p>	<p><i>*Shopping events exclusively for opioid of interest (12 months)</i></p> <p>Tapentadol: 0.6%</p> <p>Oxycodone: 28%</p> <p>-<i>Mean (SD) days to shopping event (12 months)</i></p> <p>Tapentadol: 180.0 (104.6)</p> <p>Oxycodone: 156.1 (100.9)</p>

		geographic area of pharmacy, prescriber specialty.			
Cepeda <sup>9</sup> 2013 US (2008 to 18 months after index drug dispensing)	Compare distance travelled to fill opioid prescriptions for shoppers and non-shoppers.	<b>A) Cohort</b> (N=10,910,451): ≥3 opioid dispensings; 18 months of data post-index prescription.	1) <i>Opioid shopper</i> : ≥1 days overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (18 months) <b>A)</b> 0.7% (n=75,215); accounted for 8.6% of all dispensed opioids 2) <i>Proportion of heavy shoppers</i> : ≥5 shopping episodes (18 months) <b>A)</b> 0.1% (n=9,435)	* <i>Median miles [km] travelled to fill opioid prescriptions</i> (18 months) Non-shoppers: 0 [0 km] Shoppers: 83.8 [134.9 km] Heavy shoppers: 199.5 [321.1 km] * <i>Median opioid dispensings</i> Non-shoppers: 6 Shoppers: 39 Heavy shoppers: 390	* <i>Proportion of users with opioid dispensings from ≥2 states</i> (18 months) Non-shoppers: 4.2% Shoppers: 19.3% Heavy shoppers: 22.4%
Dormuth <sup>10</sup> 2012 Canada (1993-1997)	Determine if implementing a real-time centralised prescription network (RTCP) reduced rate of potentially inappropriate BZDs and opioid dispensings.	<b>Cohort</b> : ≥1 opioid (O) or BZD dispensings for ≥30 tablets <b>A) O – Social assistance</b> (N=86,704): users receive social assistance <b>B) BZD – Social assistance</b> (N=47,983): users receive social assistance <b>C) O – aged ≥65 years</b> (N=199,497)	1) <i>Proportion of inappropriate dispensings</i> : ≥2 prescribers and ≥2 dispensing pharmacies for ≥30 tablet dispensings (7 days) <b>A)</b> 3.2% (n dispensings not reported) <b>B)</b> 1.2% (n dispensings not reported) <b>C)</b> 0.2% (n dispensings not reported) <b>D)</b> 0.6% (n dispensings not reported)	* <i>Relative change in inappropriate dispensings</i> : post RTCP implementation (30 months) <b>A)</b> -32.8% <b>B)</b> -48.6% <b>C)</b> -40.1% <b>D)</b> -42.4% * <i>Absolute change in inappropriate dispensings per month</i> <b>A)</b> -1.1% <b>B)</b> -0.5% <b>C)</b> -0.3% <b>D)</b> -0.1%	*RTCP implementation associated with large, immediate and sustained reductions in inappropriate opioid and BZD dispensings. *Inappropriate NSAIDs use (comparator drug) was infrequent and did not change during this time period.

		<b>D) BZD – aged ≥65 years (N=150,699)</b>			
Feroni <sup>11</sup> 2005 France (Oct 2001- Nov 2002)	Investigate GPs attitudes towards buprenorphine maintenance treatment (BMT) and their BMT patients' propensity to doctor shop (opioid).	<b>A) Cohort</b> (N not reported): BMT patients of 345 GPs who participated in a random telephone survey. All GP's BMT patients' data then matched to health insurance data.	No threshold of misuse defined.	*On average, BMT users access 3.1 prescribers in 12 months (range: 1-13). *Doctor shopping was lower for persons starting BMT on ≥8 mg/day, than those who were prescribed <8 mg/day. *Patients whose doctors always or often collaborate with a specialised network/care center had a higher number of prescriptions.	*Doctor shopping correlated with high mean prescriptions per user and shorter average duration of BMT. *Socioeconomic characteristics strongly associated with doctor shopping: more physicians per km <sup>2</sup> ; fewer people per household; higher unemployment or blue collar workers.
Frauger <sup>12</sup> 2009 France (2001 and 2006)	Estimate clonazepam (BZD) deviant behaviour, trends in deviant behaviour and characteristics of deviants.	<b>A) Cohort</b> (N=26,480): ≥1 clonazepam dispensings.	1) <i>Deviant group</i> : defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings, and total quantity dispensed (9 months) <b>A) Deviant user</b> : 1.1% (n=292) <i>'More deviant' user</i> : 0.07% (n=19)	* <i>Mean (SD) dispensing pharmacies</i> (9 months) Deviant: 6.4 (2.8) More deviant: 16.6 (4.3) All other persons: 1.4 (0.7) * <i>Mean (SD) prescribers</i> (9 months) Deviant: 4.6 (2.2); More deviant: 11.6 (3.7) All other persons: 1.5 (0.8) * <i>Mean (SD) dispensing episodes</i> (9 months) Deviant: 21.1 (8.3) More deviant: 65.0 (31.4)	* <i>Deviant group characteristics</i> : younger, male and associated with higher: use of BZDs and buprenorphine; number of prescribers, dispensing pharmacies, deliveries and total DDD dispensed. *The prevalence of deviant behaviour increased from 0.9% in 2001 to 1.4% in 2006. *Proportion of clonazepam dispensed to

				All other persons: 6.0 (3.0) *Mean (SD) sum of DDD dispensed (9 months) Deviant: 392.1 (200.3) More deviant: 1379.7(1014.1) All other persons: 54.6 (51.3)	deviant group increased from 7.8% (2001) to 9.5% (2009).
Frauger <sup>13</sup> 2011 France (2005-2008)	Describe patterns of methylphenidate (CNS stimulant) use and rates of abuse and diversion.	<b>A) Cohort</b> (N=3,574): ≥1 methylphenidate dispensings.	1) <i>Deviant group</i> : defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings, and total quantity dispensed (9 months) <b>A) 1.1%</b> (n=40)	*Mean (SD) dispensing pharmacies (9 months) Deviant: 11.0 (4.9) All other persons: 1.3 (0.6) *Mean (SD) prescribers (9 months) Deviant: 12.0 (4.4); All other persons: 1.8 (0.9) *Mean (SD) dispensing episodes (9 months) Deviant: 41.9 (14.7) All other persons: 6.4 (4.5)	*Mean (SD) sum of DDD dispensed (9 months) Deviant: 1707.6 (585.3) All other persons: 170.5 (150.6) *Proportion of deviant behaviour increased over study period, peak of 2.0% in 2007. *Deviant group characteristics: higher utilisation rates of BZD, AD, antipsychotic or opioid maintenance therapy.
Fredheim <sup>14</sup> 2009 Norway (2004-2006)	Identify 'problematic' codeine (opioid) prescription patterns.	<b>A) Naïve users</b> (N=222,929): ≥1 codeine dispensings in 2005. Excluded: prescriptions with incomplete identifiers or prescribed for	1) <i>High user</i> : dispensed >365 DDD of codeine (12 months) <b>A) 0.03%</b> (n=64) <b>B) 5.8%</b> (n=9,384) • <i>In high users</i> : dispensed >100 DDD of BZDs (12 months) Naïve users: 29.7% (n=19)	*Persons with >730 DDD per year of codeine frequently co-medicated with other drugs including BZDs (66%) and carisoprodol (45%). *0.5% of persons	

		cancer. <b>B) Old users</b> (N=162,261): A) and ≥1 codeine dispensings in 2004.	Old users: 50.5% (n=4,738) • <i>In high users: dispensed &gt;15 DDD of carisoprodol (12 months)</i> Naïve users: 18.8% (n=12) Old users: 30.2% (n=2,838) • <i>In high users: dispensed &gt;730 DDD of codeine (12 months)</i> Naïve users: 1.6% (n=1) Old users: 19.0% (n=1,786)	prescribed codeine developed serious problematic use.	
Gilson <sup>15</sup> 2012 US (2000-2006)	Investigate if changes to prescription monitoring program influences: i) prescribing rate for nine schedule II long- (LA) or short-acting (SA) opioids, or ii) incidence of multiple provider episodes (MPEs).	<b>A) Cohort</b> (N not reported): inclusion/exclusion criteria not specified. Prescription level data (N=15,506,651)	1) <u>Prescriptions</u> involved in MPEs: ≥2 prescribers for same opioid and ≥2 dispensing pharmacies (30 days) 9.6% (n prescriptions=1,488,639)	* <u>Prescriptions</u> dispensed involving MPEs (time period not reported) SA hydromorphone: 15.2% SA fentanyl: 11.4% SA oxycodone: 10.9% SA morphine: 10.0% LA oxycodone: 8.7% Methadone: 8.6% LA morphine: 8.5% LA fentanyl: 8.1% Meperidine: 7.0%	*Policy change increased rate of MPEs involving all opioids. *Replacing triplicate forms with a secure tamper resistant form increased prescribing rates for SA hydromorphone, meperidine, SA oxycodone. Prescribing rates unchanged for SA or LA fentanyl, methadone, SA or LA morphine and LA oxycodone.
Gjerdén <sup>16</sup> 2009 Norway	Investigate use and potential	<b>Cohort</b> (N=73,964): aged 18-69 <b>A)</b> (N=70,937)	1) <i>Proportion of drug volume consumed by highest 1% of users: a figure &gt;15% is a strong signal for drug</i>	* <i>Maximum number of BZD-prescribers (12 months)</i>	

(2004)	abuse of antiparkinson (AP) drugs.	<p>Dispensed any antipsychotic drug <b>B)</b> (N=2,771)</p> <p>Dispensed dopaminergic or anticholinergic AP drug reimbursed for Parkinson's disease <b>C)</b> (N=213) Dispensed antipsychotic and evidence of Parkinson's disease <b>D)</b> (N=43) Dispensed anticholinergic drug, not dispensed an antipsychotic, no evidence of Parkinson's disease. Excluded if: dispensed benhexol, procyclidine or trihexyphenidyl.</p>	<p>abuse (12 months)</p> <p>Biperiden: 6.2%</p> <p>BZDs: 16.5%</p> <p>Orphenadrine: 5.4%</p> <p>2) <i>Doctor shopper</i>: ≥3 prescribers for BZD tranquilizers (12 months)</p> <p>No meaningful data derived.</p>	<p><b>A)</b> 8</p> <p><b>B)</b> 5</p> <p><b>C)</b> 3</p> <p><b>D)</b> 6</p> <p>*Antipsychotic drug-users accounted for 94% of anticholinergic use, compared to 4.3% of antipsychotic drug-users with Parkinson's disease.</p> <p>*BZD use more frequent in antipsychotic drug-users than antipsychotic drug-users with Parkinson's disease.</p> <p>*Cohort D had highest rate of BZD concomitant use.</p>	
Goodman <sup>17</sup> 2005 US (Jun 2000-Jul 2002)	Determine if a prescription review could identify cases of possible oxycodone ER abuse (opioid).	<p><b>A) Cohort</b> (N not reported): ≥1 oxycodone ER dispensing from a Veteran's Affairs (VA) facility. Case level data (N cases = 60,955)</p>	<p>Proportion of cases meeting criteria.</p> <p>1) <i>Dispensed large quantity</i>: ≥480 tablets per prescription (20 months)</p> <p><b>A)</b> 5% (n=4 cases)</p> <p>2) <i>Multiple sites</i>: prescription for same drug filled ≥10 days early from ≥2 facilities (25 months)</p> <p><b>A)</b> 24% (n=41 cases)</p>	<p>*Cases involving past/present substance abuse diagnosis per measure of misuse (time period not reported)</p> <p>Dispensed large quantity: 3% (n=2 cases)</p> <p>Multiple sites: 5% (n=8</p>	<p>*Multiple VISNs: <u>doctor</u> aberrant prescribing not defined (10 months) 2%</p> <p>*The prevalence of aberrant drug-related behaviour of multiple sites or multiple VISNs</p>

			<p>3) <i>Multiple Veterans Integrated Service Networks (VISNs)</i>: prescription for same drug filled <math>\geq 10</math> days early from <math>\geq 2</math> VISNs (10 months)  <b>A)</b> 15% (n=6 cases)  4) <i>High usage</i>: <math>\geq 480</math> tablets per prescriptions, high dosage (320 mg daily), or frequent dosing intervals (every 4-6 hours): extent of misuse not reported  5) <i>Early refills</i>: <math>\geq 2</math> consecutive early refills from <math>\geq 2</math> providers: extent of misuse not reported  6) <i>Large total quantity</i>: <math>\geq 480</math> tablets total per month: extent of misuse not reported</p>	<p>cases)  Multiple VISNs: 5% (n=2 cases)    <u>Doctor's</u> aberrant prescribing pattern as indicator.  *<u>Doctors</u> prescribed large quantity: <math>\geq 480</math> tablets per prescription (20 months) 12% (n=10 cases)  *<u>Multiple sites</u>: <u>doctor</u> aberrant prescribing not defined (25 months) 2% (n=3 cases)</p>	<p>decreased over the review periods.</p>
Hall <sup>18</sup> 2008 US (2006)	Evaluate characteristics of persons dying from unintentional pharmaceutical overdose (controlled substances), types of drugs involved and the role of drug abuse in	<p><b>A) Cohort</b> (N=295): died of unintentional drug poisoning according to death certificate in 2006.  Excluded: no autopsy performed; toxicology tests not performed by Office of Medical Examiner; overdose due exclusively to illicit drugs, over the counter products and/or alcohol.</p>	<p>1) <i>Doctor shopper</i>: <math>\geq 5</math> prescribers of controlled substances (12 months)  <b>A)</b> 21.4% (n=63)</p>	<p>*<i>Diverters</i>: pharmaceuticals used without a prescription record (12 months)  <b>A)</b> 63.1% (n=186)  *<i>Diverter and doctor shopper</i> (12 months)  <b>A)</b> 8.1% (n=24)  *<i>Deaths involving specific drug classes</i> (12 months)  Opioid analgesic: 93.2%  Psychotherapeutic: 48.8%  Other prescription drug (butalbital, carisoprodol,</p>	<p>*Unintentional overdose death rate: 16.2/100,000  *Doctor shopping associated with: being female (OR 2.2); aged 35-44 years (OR 2.0); previous overdose (OR 2.8).  *Diversion behaviour associated with: 18-24 age group (OR 12.1) never marrying (OR 2.8); history of substance abuse (OR 1.8); non-</p>

	deaths.			cyclobenzaprine, diltiazem, phenytoin, promethazine): 11.2%	medical route of pharmaceutical administration (OR 1.9) or illicit drug use (OR 2.1).
Han <sup>19</sup> 2012 US (2005-2007)	Examine effect of individual and county related factors on use of multiple prescribers and/or pharmacies for prescription opioids.	<b>A) Cohort</b> (N=1,057,012): ≥1 opioid dispensings per year (2005 to 2007). Excluded if: incomplete/implausible prescription; commercial transaction; non-standard route of administration for chronic pain users; drug use by age group not associated with chronic pain or obtaining drugs through office interactions.	No threshold of misuse defined.	<i>*Number of prescribers</i> (12 months) <b>A) Mean</b> (range): 2.1 (1-158) 1 prescriber: 50.7% (n=536,408) 2-5 prescribers: 45.1% (n=476,843) ≥6 prescribers: 4.1% (n=43,761) <i>*Number of dispensing pharmacies</i> (12 months) <b>B) Mean</b> (range): 1.8 (1-100) 1 pharmacy: 59.0% (n=623,357) 2-5 pharmacies: 38.9% (n=411,704) ≥6 pharmacies: 2.1% (n=21,951) <i>*Higher number of prescribers and dispensing pharmacies associated with: younger age (18-74), being female, living in a</i>	<i>*Physician availability was the most robust predictor, i.e. as number of physicians increased so did number of prescribers and dispensing pharmacies.</i> <i>*Individuals who use both schedule II and III opioids visited multiple prescribers and multiple pharmacies more often than those who used opioids from a single schedule.</i> <i>*Higher use of multiple prescribers and pharmacies associated with: ethnicity, educational attainment, median household income and physician availability.</i>

				county with more licensed physicians and surgeons.	
Hartz <sup>20</sup> 2009 Norway (2004-2007)	Examine association between disability pensioners using BZD and aspects of problematic use.	<b>A) Cohort</b> (N=19,520): aged ≤61 years; ≥1 BZD dispensing; health survey data linked to national prescription database. Excluded if: reimbursed for cancer drugs; died/emigrated prior to 2004; BZD user at survey baseline; wrote trade names for BZD in survey; missing disability status.	<i>1) Long term user: dispensed ≥1 BZD each year between 2004 and 2007 (48 months)</i> <b>A) 2.2%</b> (n=425)	*In long term users, median BZD use was higher in disability pensioners (50 DDD) than non-disability pensioners (20 DDD). *When controlling for other factors, long term use of BZD is more prevalent in disability pensioners than non-disability pensioners (OR 2.5).	*Predictors of long-term BZD use: being female and increasing age. *Use of BZD and other potentially addictive drugs (z-drugs, opioids and carisoprodol) increased over the 4 years.
Hoffman <sup>21</sup> 2003 US (1998-Mar 2000)	Evaluate effectiveness of physician alert to reduce patients' excessive use of prescription drugs and decrease costs to the third party	<b>A) Control</b> (n=89): ≥1 alert. <b>B) Excessive users</b> (n=94): letter sent to physician; user has ≥3 alerts in 3 months (alerts relate to number of prescribers, pharmacies and volume of drug dispensed); no concurrent	<i>1) Recurrent excessive users: ≥2 letters sent out to physician (6 months)</i> <b>B) 29.8%</b> (n=28)	* <i>Number of prescribers</i> (3 months) Pre-intervention mean (SD) to post-intervention mean (SD) [% change] <b>A) 5.3</b> (2.4) to 1.4 (2.4) [-22.0%] <b>B) 6.4</b> (3.6) to 2.2 (3.3) [-28.0%] * <i>Number of prescriptions</i> (1 month) <b>A) 13.4</b> (3.5) to 3.7 (4.7) [-28.4%]	* <i>Prescription drug cost</i> (1 month) <b>A) \$460.15</b> (\$335.00) to \$39.07 (\$331.00) [-17.9%] <b>B) \$480.28</b> (\$393.00) to \$118.38 (\$296.00) [-23.1%] * <i>Medical cost</i> (12 months) <b>A) \$8811.90</b> to \$970 [not reported] <b>B) \$9115.96</b> to \$1413.00

	payer (controlled substances schedule II to IV).	prescription drug use indicative of cancer, HIV infection or renal failure. Excluded if: Medicare user; <6 of collected data. Cohorts matched on total number of prescriptions and number of prescriptions with abuse potential.		<b>B)</b> 13.7 (6.4) to 5.0 (4.4) [38.1%] <i>*Number of high abuse prescriptions (1 month)</i> <b>A)</b> 5.5 (2.1) to 2.0 (2.6) [-33.6%] <b>B)</b> 6.0 (2.8) to 3.1 (4.6) [-45.5%]	[not reported] *23% of users whose physicians received letters did not show any change in dispensing patterns. *Authors attributed control group results to 'regression toward the mean'.
Katz <sup>22</sup> 2010 US (Jul 1995- Jun 2006)	Evaluate trends in schedule II opioid prescribing and dispensing.	<b>A) Cohort</b> (N=562,592): ≥1 opioid dispensings in 2006. Excluded if: entry missing prescriber number, date filled, prescription number, quantity, national drug code, days of supply, valid date of birth or customer ID.	1) <i>Questionable activity</i> : ≥3 prescribers and ≥3 dispensing pharmacies (12 months) % persons; % prescriptions; % dosage units <b>A)</b> 1.6% (n=8,797); 7.7% (n=112,381); 8.5% (n=7,622,840) 2) <i>Preferred indicator: Questionable activity</i> : ≥4 prescribers and ≥4 dispensing pharmacies (12 months) <b>A)</b> 0.5% (n=2,748); 3.1% (n=45,102); 3.1% (n=2,805,613) 3) <i>Questionable activity</i> : ≥5 prescribers and ≥5 dispensing pharmacies (12 months) <b>A)</b> 0.2% (n=1,149); 1.5% (n=22,075); 1.4% (n=1,247,666) 4) ≥1 <i>early refills</i> : two consecutive	<i>*Number of prescribers (12 months)</i> <b>A)</b> Mean (SD): 1.4 (0.93) 1 prescriber: 78.9% (n=443,956) 2 prescribers: 13.4% (n=75,191) 3 prescribers: 4.4% (n=24,919) 4 prescribers: 1.8% (n=9,980) 5 prescribers: 0.8% (n=4,274) 6 prescribers: 0.3% (n=1,887) 7 prescribers: 0.2% (n=1,025) 8 prescribers: 0.1%	<i>*Number of dispensing pharmacies (12 months)</i> <b>A)</b> Mean (SD): 1.1 (0.52) 1 pharmacy: 90.6% (n=509,818) 2 pharmacies: 6.9% (n=38,865) 3 pharmacies: 1.6% (n=8,870) 4 pharmacies: 0.5% (n=2,917) 5 pharmacies: 0.2% (n=1,138) 6 pharmacies: 0.1% (n=464) 7 pharmacies: 0.04% (n=248) 8 pharmacies: 0.02%

			<p>prescriptions for same drug with number of days between prescriptions being &gt;10% lower than number of days of supply in first prescription, i.e. if prescription for 30 days, second prescription filled &lt;27 days after first dispensing) (time period varied based on length of prescription)  Mean (SD): 0.1 (0.67)  <b>A) 6.9% (n=38,819)</b></p>	<p>(n=543)  9 prescribers: 0.1% (n=296)  ≥10 prescribers: 0.1% (n=520)  *76.9% of users with one prescriber accessed one pharmacy; 0.1% of users with one prescriber accessed ≥4 dispensing pharmacies.  *Among persons using ≥5 prescribers, 14.1% used ≥4 dispensing pharmacies.  *Among persons using ≥10 prescribers, 69.2% used ≥4 dispensing pharmacies.  *11% of total population received ≥1 schedule II opioid in 2006.</p>	<p>(n=108)  9 pharmacies: 0.01% (n=76)  ≥10 pharmacies: 0.02% (n=87)  *Rate of questionable activity increased between 1996-2002 and decreased between 2002-2006, despite an increase in opioid prescribing.  *SA oxycodone was the opioid most associated with questionable activity.</p>
Logan <sup>23</sup> 2013 US (2009)	Determine prevalence of opioid misuse and the inappropriate prescription practices by emergency department (ED)	<b>A) Cohort</b> (N=400,288): aged 18-64; ≥1 opioids dispensed same day as ED visit that was not part of a hospital admission. Excluded if: incomplete information; claims for services which	<p>1) ≥2 overlapping ED opioid prescriptions: overlapping by ≥7 days (12 months)  <b>A) 2.1% (n=8,229)</b>  2) Overlapping ED opioid and BZD prescriptions: overlapping by ≥7 days (12 months)  <b>A) 1.0% (n=3,867)</b>  3) ≥1 incidents of LA/ER opioid dispensed for acute pain condition (12</p>	<p>*<u>Prescriptions overlapped with another LA opioid prescriptions</u>: overlapping by ≥7 days (12 months)  <b>A) 14.6%</b>  *≥2 opioid-related ED presentations (12 months)  <b>A) 8% (n=32,024)</b>  *Number of ED opioid prescriptions (12 months)</p>	<p>*A higher proportion of females (11.5%) had at least one indicator of potentially inappropriate prescribing or misuse, compared to males (9.0%).</p>

	providers.	could not render opioids; tests not confirming diagnostic information; not continuously enrolled in health plan for 2009; or treatment for cancer pain determined by ICD-9 diagnosis for cancer.	months) <b>A)</b> 0.1% (n=565) 4) <i>Dispensed high opioid doses from ED</i> : daily dose of ≥100 morphine milligram equivalent (12 months) <b>A)</b> 7.8% (n=31,117)	<b>A)</b> 1 prescription: 91.0% 2 prescriptions: 7.0% ≥3 prescriptions: 2.0%	
Mailloux <sup>24</sup> 2010 US (Jul 1998– Aug 1999)	Identify persons abusing controlled substances (opioids, BZDs, and CNS stimulants) through a decision support tool. Abuse determination based on number of prescribers, pharmacies, volume of drug	<b>A) Intermediate abusers</b> (N=85): letter sent to physician to alert them to their patients' behaviour <b>B) Abusers</b> (N=39): no change from 'intermediate abuser' behaviour within 6 months, individual is 'locked-in,' i.e. for 2 years one prescriber and one dispensing pharmacy. Excluded if: 'lock-in' required informed consent, part of mental health commitment or condition of probation/parole.	1) <i>Shopping behaviour</i> : drug obtained by 'multiple providers and pharmacies' (6 and 2 months) <i>i)</i> Mean (SD) days of overlapping prescriptions (6 months) <b>A)</b> 155.8 (103.1) <b>B)</b> 768.2 (609.2) <i>ii)</i> Mean (SD) days of overlapping prescriptions (2 months) <b>A)</b> 70.8 (55.4) <b>B)</b> 350.8 (246.1) 2) <i>Early refill</i> : one drug obtained from one physician and multiple pharmacies within 50% of the days' supply of the first prescription (6 and 2 months) <i>i)</i> Mean (SD) episodes (6 months) <b>A)</b> 1.9 (2.5) <b>B)</b> 5.9 (13.4) <i>ii)</i> Mean (SD) episodes (2 months)	* <i>Mean (SD) duplicate prescription score</i> : number of duplicate prescriptions (controlled substance obtained from different prescribers/pharmacies on the same day) (time period not reported) <b>A)</b> 0.3 (0.6) <b>B)</b> 1.2 (1.5) * <i>Mean (SD) dispensing pharmacies</i> (time period not reported) <b>A)</b> 4.2 (1.8) <b>B)</b> 9.9 (4.3) * <i>Mean (SD) prescribers</i> (time period not reported) <b>A)</b> 4.8 (2.7) <b>B)</b> 12.2 (6.5)	* <i>Mean controlled substances claims</i> (time period not reported) <b>A)</b> 22.3 (10.4) <b>B)</b> 48.7 (18.6) *Overall the classification rate is 95.3%. (Sensitivity: 87.2%, specificity: 96.5%.) *Number of dispensing pharmacies was the best predictor of abuse of controlled substances.

	dispensed and medical diagnosis.		<b>A) 0.6 (1.0)</b> <b>B) 3.1 (6.6)</b>		
Martin <sup>25</sup> 2011 US (2000-2005)	Report rates of opioid misuse, discontinuation (≥182 days of no opioid use), and identify factors associated with discontinuation.	<b>A) Commercially insured</b> (N=23,41): ≥1 chronic opioid use episode, i.e. >90 days of opioids supplied in any 6 month period between Mar 2001-Dec 2004, continuous enrolment for 12 months pre-and post-index date (first opioid dispensing), identified in HealthCore dataset. <b>B) Publically insured</b> (N=6,848): A) but identified in Arkansas Medicaid.	1) <i>Opioid misuse score</i> : based on excess days supplied short- and long-acting opioids, number of dispensing pharmacies, and number of prescribers (6 months) Score 0-1: no misuse <b>A) 83.2%</b> (n=19,474) <b>B) 87.7%</b> (n=6,003) Score 2-3: possible misuse <b>A) 14.5%</b> (n=3,399) <b>B) 10.9%</b> (n=747) Score ≥4: probable misuse <b>A) 2.2%</b> (n=523) <b>B) 1.4%</b> (n=98)	* <i>Prevalence of opioid abuse disorder</i> (time period not reported) <b>A) 0.6%</b> (n=130) <b>B) 0.5%</b> (n=36) *Approximately 1/7 persons potentially misuse opioids. *Commercially insured cohort: persons with possible or probable opioid misuse were 20% less likely to discontinue opioids than those with no indication of opioid misuse.	
McDonald <sup>26</sup> 2013 US (2008)	Estimate prevalence of users obtaining opioid prescriptions from different physicians.	<b>A) Cohort</b> (N='13.6 million'): ≥1 opioid dispensings in first 60 days of 2008.	1) <i>Extreme outlying population</i> : determined by latent class analysis based on method of payment, gender, age (10 months) <b>A) 0.7%</b> (n≈95,200), accounting for 1.9% of dispensed drug.	* <i>Number of prescribers for opioid after first 60 days of 2008</i> (10 months) 1 prescriber: 31% 2 prescribers: 14% 3-4 prescribers: 8.6% (inferred) 5-9 prescribers: 3% 10-19 prescribers: 0.4%	*Users 'aged mid to late 20s were 10 times more likely to fit the extreme profile than users double their age'. *In the extreme population, the average number of prescribers increased with age until age 40, after which it

				≥20 prescribers: 0.04% *Mean number of prescribers for extreme population (10 months): 10.4	declined.
Nordmann <sup>27</sup> 2013 France (2008)	Describe and compare opioid abuse using doctor shopping to estimate abuse in three French regions.	<p><b>A) PACA</b> (N=885,941): ≥1 opioid dispensings; resident of Provence-Alpes-cote d’Azur (PACA)</p> <p><b>B) RA</b> (N=945,102): A) except resident of Rhone Alps (RA).</p> <p><b>C) MP</b> (N=386,834): A) except resident of Midi-Pyrenees (MP).</p> <p><b>D) Entire cohort</b> (N=2,217,877): A) + B) + C)</p>	<p>1) <i>Doctor shopping quantity (DSQ)</i>: amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months)</p> <p><b>A)</b> 213.3 DDD/1000 population</p> <p><b>B)</b> 115.1 DDD/1000 population</p> <p><b>C)</b> 106.2 DDD/1000 population</p> <p><b>D)</b> 150.5 DDD/1000 population</p> <p>Drug class: DSQ (DDD/1000 population) (% of all dispensed drug)</p> <p>Weak opioid analgesics: 75.5 (50.2%)</p> <p>OMT opioids: 55.3 (36.7%)</p> <p>Strong opioid analgesics: 19.7 (13.1%)</p> <p>2) <i>Doctor shopping indicator (DSI)</i>: proportion of total drug dispensed obtained by overlapping prescriptions from ≥2 prescribers (12 months). DSI &lt;1% is not a signal for abuse.</p> <p>Drug class: DSI</p> <p>OMT: 6.2%</p> <p>Strong opioid analgesics: 5.0%</p> <p>Weak opioid analgesics: 1.1%</p>	<p>*DSQ by opioid (12 months)</p> <p>Drug: DSQ (DDD/1000 population)</p> <p><b>D) Buprenorphine (OMT):</b> 50.3</p> <p>Dextropropoxyphene: 27.6</p> <p>Codeine: 24.1</p> <p>Tramadol: 23.3</p> <p>Morphine: 17.8</p> <p>Methadone: 4.9</p> <p>Oxycodone: 1.5</p> <p>Dihydrocodeine: 0.5</p> <p>Buprenorphine (analgesic): 0.2</p> <p>Hydromorphone: 0.2</p>	<p>*Specific opioids with DSI≥1% (12 months)</p> <p><b>D) Buprenorphine (OMT):</b> 8.0%</p> <p>Morphine: 5.5%</p> <p>Dihydrocodeine: 3.7%</p> <p>Buprenorphine (analgesic): 2.9%</p> <p>Oxycodone: 2.7%</p> <p>Codeine: 2%</p> <p>Methadone: 1.9%</p> <p>Hydromorphone: 1.8%</p> <p>Tramadol: 1.1%</p> <p>*DSQ was 2-fold higher in PACA than RA and MP.</p> <p>*Tramadol and dextropropoxyphene DSI show a very low signal of abuse.</p>
Parente <sup>28</sup> 2004 US	Develop indicators of controlled	<p><b>A) Cohort 1</b> (N=2,927,237).</p> <p><b>B) Cohort 2</b></p>	<p>1) ≥6 prescribers of same drug (time period not reported)</p> <p><b>A)</b> 0.2% (n=6,148)</p>	<p>*These measures are not a direct measure of misuse, but direct attention to</p>	

(2000)	substance misuse for general population (excluding persons with $\geq 3$ prescriptions for injectable opioid without a cancer diagnosis in 12 months and persons dispensed a BZD or opioid with a substance abuse diagnosis)	(N=782,800). Inclusion/exclusion criteria not specified.	<p><b>B)</b> 0.3% (n=1,957)</p> <p>2) <math>\geq 4</math> <i>dispensing pharmacies for same drug</i> (time period not reported)</p> <p><b>A)</b> 0.1% (n=3,806)</p> <p><b>B)</b> 0.1% (n=1,096)</p> <p>3) <math>\geq 4</math> <i>prescriptions of carisoprodol</i> (6 months)</p> <p><b>A)</b> 0.1% (n=3,805)</p> <p><b>B)</b> 0.1% (n=862)</p> <p>4) <i>Continuous overlap of <math>\geq 2</math> different BZDs for <math>\geq 90</math> days</i> (time period not reported)</p> <p>i) when 1 BZD is alprazolam</p> <p><b>A)</b> 0.1% (n=1,757)</p> <p><b>B)</b> 0.1% (n=548)</p> <p>ii) when 1 BZD is clonazepam</p> <p><b>A)</b> 0.01% (n=147)</p> <p><b>B)</b> 0.01% (n=58)</p> <p>iii) when 1 BZD is diazepam</p> <p><b>A)</b> 0.003% (n=88)</p> <p><b>B)</b> 0.004% (n=32)</p> <p>5) <math>\geq 4</math> <i>grams/day of acetaminophen</i> (time period not reported)</p> <p><b>A)</b> 0.03% (n=878)</p> <p><b>B)</b> 0.01% (n=79)</p> <p>6) <math>\geq 2</math> <i>prescriptions for meperidine hydrochloride with <math>&gt;2</math> days' supply</i> (time period not reported)</p> <p><b>A)</b> 0.02% (n=585)</p> <p><b>B)</b> 0.02% (n=157)</p>	potential problems to determine if intervention is needed.	
--------	--	--	---	--	--

			<p>7) <math>\geq 4</math> prescriptions of butorphanol (6 months)  <b>A)</b> 0.02% (n=585)  <b>B)</b> 0.02% (n=157)</p> <p>8) Overlap of <math>\geq 2</math> different sustained release or LA opioids for <math>\geq 90</math> consecutive days (time period not reported)  <b>A)</b> 0.001% (n=30)  <b>B)</b> 0.001% (n=8)</p>		
Pauly <sup>29</sup> 2011 France (2006)	Compare two methods to measure deviant behaviour when obtaining high dosage buprenorphine (HDB) (opioid).	<b>A) Cohort</b> (N=6,519): $\geq 1$ dispensing of HDB.	<p>1) <i>Deviant persons</i>: defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings, and total quantity dispensed (9 months).  <b>A)</b> 6.0% (n=390)  <i>'More deviant' persons</i>: 0.3% (n=21)</p> <p>2) <i>Proportion of dispensed HDB obtained by DSI</i>:  <i>Deviant</i>: 40% (i.e. 60% not obtained by DSI)  <i>More deviant</i>: 72% (i.e. 18% not obtained by DSI)  <i>Entire cohort</i>: 13.2%</p>	<p>*<i>Mean (SD) prescribers</i> (9 months)  Deviant: 6.5 (2.2)  More deviant: 16.4 (5.7)</p> <p>*<i>Mean (SD) dispensing pharmacies</i> (9 months)  Deviant: 8.2 (3.3)  More deviant: 27.5 (9.5)</p> <p>*<i>Mean (SD) dispensings</i> (9 months)  Deviant: 36.9 (16.7)  More deviant: 90.0 (32.0)</p>	<p>* <i>Mean (SD) total quantity dispensed (mg)</i> (9 months)  Deviant: 6,815 (4,462)  More deviant: 33,720 (14,432)</p> <p>*Deviant group are: younger, male, dispensed a higher proportion of flunitrazepam, bromazepam, clonazepam and ADs.</p>
Pauly <sup>30</sup> 2011 France (2008)	Analyze and compare diversion and abuse of 14 BZDs through a multi-	<b>A) Cohort</b> (N not reported): $\geq 1$ BZD dispensings.	<p>1) <i>Deviant persons</i>: defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings, and total quantity dispensed (9 months).  <i>BZD with highest % of deviant users</i>:</p>	<p>*<i>Proportion of deviant users per BZD</i>:  Oxazepam: 0.4%  Clonazepam: 0.3%  Diazepam: 0.3%  Zolpidem: 0.3%</p>	<p>*<i>BZDs with DSI<math>\geq 1</math></i>: rate of &lt;1% does not constitute a signal for abuse (12 months)  Clonazepam: 2.6%  Zolpidem: 2.5%</p>

	indicator approach.		Flunitrazepam: 9.1% 2) <i>Doctor shopping indicator (DSI)</i> : proportion of total drug dispensed obtained by DSQ: amount of excess drug obtained by overlapping prescriptions and $\geq 2$ prescribers (12 months). <i>BZD with highest DSI</i> : Flunitrazepam: 27.0%	Bromazepam: 0.3% Lormetazepam: 0.2% Clorazepate: 0.2% Alprazolam: 0.2% Lorazepam: 0.2% Zopiclone: 0.1% Prazepam: 0.04% Tetrazepam: 0.03% Nordazepam: 0.03%	Oxazepam: 2.3% Diazepam: 2.2% Alprazolam: 1.7% Bromazepam: 1.7% Lormetazepam: 1.5% Lorazepam: 1.3% Clorazepate: 1.1% Zopiclone: 1.1%
Pauly <sup>31</sup> 2012 France (2006-2008)	Compare doctor shopping indicator (DSI) across 14 BZDs and 10 opioids [prescribed for analgesic or opioid maintenance treatment (OMT)].	<b>A) Cohort</b> (N not reported): inclusion/exclusion criteria not specified.	1) <i>DSI</i> : proportion of total drug dispensed obtained by DSQ (DSQ: amount of excess drug obtained by overlapping prescriptions from $\geq 2$ prescribers) (time period not reported). DSI <1% is not a signal for abuse. <i>Drug with highest DSI</i> : Buprenorphine (OMT): 12.5%	* <i>Other drugs with DSI</i> $\geq 1\%$ (time period not reported) Opioid (OMT): 7.2% Morphine: 6.2% Buprenorphine (analgesic): 3.9% Methadone: 3.3% BZD: 1.9% Oxycodone: 1.9%	*BZDs are prescribed at a high rate but have a low rate of abuse/diversion. *Opioids (OMT) prescribed at low rate but have a high level of abuse/diversion.
Pearson <sup>32</sup> 2006 US (1988-1995)	Examine impact of the triplicate prescription program (TPP) on potentially problematic	<b>A) Entire cohort</b> (N=124,867): $\geq 19$ years; Medicaid enrollee for $\geq 10$ out of 12 months prior to TPP; dispensed $\geq 1$ BZDs. (B+C+D+E) Cohort stratified by	1) <i>Pharmacy hoppers</i> : dispensed same BZD from $\geq 2$ pharmacies (7 days) <b>A)</b> 1.6% (n=1,955) <b>B)</b> 1.3% (n=588) <b>C)</b> 1.7% (n=740) <b>D)</b> 1.4% (n=169) <b>E)</b> 1.9% (n=458) 2) <i>Problematic use of BZD</i> : BZD use	*After introduction of TPP there was a sudden and sustained reduction in BZD use and potentially problematic use in all New York neighborhoods. *Across all practices and pharmacy locations black	

	BZD use by race.	predominant racial neighborhood composition <b>B) White</b> (N=45,222) <b>C) Mixed</b> (N=43,520) <b>D) Black</b> (N=12,054) <b>E) Hispanic</b> (N=24,071)	was >2 times MRDD OR duration of BZD treatment >120 days <b>A) 40.2%</b> (n=50,197) 3) <i>Any potentially problematic BZD use:</i> (1 or 2) pharmacy hopper or problematic use of BZD <b>A) 42.8%</b> (n=53,444) <b>B) 51.6%</b> (n=23,335) <b>C) 41.1%</b> (n=17,887) <b>D) 34.5%</b> (n=4,159) <b>E) 33.7%</b> (n=8,112)	enrollees were most likely, white enrollees least likely, to experience reductions in access to BZDs. * '>83%' of baseline pharmacy hoppers discontinued post-TPP.	
Peirce <sup>33</sup> 2012 US (Jul 2005-2007)	Compare doctor and pharmacy shopping behaviours between deceased and living persons, and identify factors that predict a drug-related death (controlled substances).	<b>A) "Living" persons cohort</b> (N=1,049,205): ≥18 years; dispensed ≥1 schedule II-IV controlled substance between Jul 2005-Dec 2007. <b>B) Decedent cohort</b> (N=698): A) and death recorded as drug-related by the medical examiner in the Forensic Drug Database. <b>C) Entire cohort</b> (N=1,049,903): A) + B)	1) <i>Pharmacy shopper:</i> ≥4 dispensing pharmacies (6 months) <b>A) 1.3%</b> (n=13,619) <b>B) 17.5%</b> (n=122) <b>C) 1.3%</b> (n=13,741) • <i>In pharmacy shoppers (entire cohort), proportion of doctor shoppers</i> (6 months) 55.6% (n=7,640) 2) <i>Doctor shopper:</i> ≥4 prescribers (6 months) <b>A) 3.6%</b> (n=37,594) <b>B) 25.2%</b> (n=176) <b>C) 3.6%</b> (n=37,770) • <i>In doctor shoppers (entire cohort), proportion of pharmacy shoppers</i> (6 months) 20.2% (n=7,640)	* <i>Pharmacy shoppers (entire cohort) with ≥4 prescriptions dispensed</i> (6 months) 90.0% (n=12,361) * <i>Pharmacy shoppers (entire cohort) with ≥3 controlled substances dispensed</i> (6 months) 50.3% (n=6,918) * <i>Doctor shoppers with ≥4 prescriptions dispensed</i> (6 months) 82.6% (n=31,180) * <i>Doctor shoppers (entire cohort) with ≥3 controlled substances dispensed</i> (6 months) Doctor shopper: 49.2%	*86% of decedent cohort deaths were due to a controlled substance. * Predictors of drug-related death: greater number of prescriptions dispensed (not defined, OR 1.14); dispensed an opioid (OR 3.40); dispensed a BZD (OR 7.21); dispensed both BZD and opioid (OR 14.92); pharmacy and doctor shopper (OR 3.59); pharmacy shopper alone (OR 3.8); doctor shopper alone (OR 2.03). * Older age (not defined) was less associated with

				(n=18,566)	drug-related death (OR 0.96).
Pradel <sup>34</sup> 2004 France (Sep 1999- Dec 2000)	Assess rates of doctor shopping for high dosage buprenorphine (HDB) maintenance therapy (opioid)	<b>A) Cohort</b> (N=2,587): ≥1 HDB dispensings; >31 days of follow up. Excluded if: insufficient number of prescriptions.	1) <i>Doctor shopper</i> : overlapping prescriptions and ≥2 prescribers (16 months) <b>A)</b> 39.5% (n=1,023) • <i>In doctor shoppers: persons dispensed ≥16 mg per day of HDB (16 months)</i> 8.5% (n=87)	* <i>Quantity HDB obtained by doctor shoppers</i> : 18.7% (1,802,806 mg) * <i>Delivered doses of HDB for doctor shoppers (mg/day)</i> : 2.2 mg	
Pradel <sup>35</sup> 2009 France (2000, 2002, 2004, 2005)	Assess the prevalence of doctor shopping for HDB (opioid) and evaluate the impact of the prescription monitoring program (PMP) for maintenance treatment.	<b>A) Cohort</b> (N=21,911): ≥2 HDB dispensings in 35 days.	1) <i>Doctor shopping quantity (DSQ)</i> : amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months). Range: 631 (2000) to 1151 (2004) grams 2) <i>Doctor shopping indicator (DSI)</i> : proportion of total drug dispensed obtained by DSQ (12 months) Range: 14.9% (2000) to 21.7% (2004)	* <i>Impact of PMP (last 6 months of 2004 to last 6 months of 2005)</i> : DSQ: 1151 grams to 858 grams. DSI: 21.7% to 16.9%. *At any given time period, approximately 200 patients (<8%) obtained 80% of HDB. *75% of users did not have a DSQ.	
Pradel <sup>36</sup> 2010 France (2003)	Assess abuse potential of eight BZDs (14 formulations)	<b>A) Cohort</b> (N=128,230): ≥1 BZD dispensings.	1) <i>Doctor shopping quantity (DSQ)</i> : amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months). Total BZD DSQ: 361,428 DDD	* <i>Volume of drug obtained by DSQ (DDD) (12 months)</i> Bromazepam 6 mg: 56,913 Clorazepate 50 mg: 36,335 Alprazolam 0.5 mg: 14,852	*For BZDs with multiple formulations, highest doses always had higher DSI/DSQ than lower doses.

	via doctor shopping.		<p><i>BZD with highest DSQ:</i> Flunitrazepam 1 mg: 108,727 DDD</p> <p><i>2) Doctor shopping indicator (DSI):</i> proportion of total drug dispensed obtained by DSQ. DSI&lt;1% does not constitute a signal for abuse (12 months)</p> <p><i>BZD with highest DSI:</i> Flunitrazepam 1 mg: 42.8%</p>	<p>Diazepam 10 mg: 11,125 Lorazepam 2.5 mg: 10,360 Clonazepam 2 mg: 7,752 Lorazepam 1 mg: 4,222 Tetrazepam 50 mg: 2,910 Clorazepate 10 mg: 2,645 Alprazolam 0.25 mg: 1,308 Diazepam 5 mg: 1,110 Clorazepate 5 mg: 401 Diazepam 1 mg: 200</p> <p><i>*Drugs with DSI ≥1% (12 months)</i> Diazepam 10 mg: 3.2% Clorazepate 50 mg: 2.7% Alprazolam 0.5 mg: 1.9% Bromazepam 6 mg: 1.9% Clonazepam 2 mg: 1.8% Lorazepam 2.5 mg: 1.1%</p>	<p>*BZDs by abuse potential: Very high: flunitrazepam 1 mg; High: diazepam 10 mg, clorazepate 50 mg; Intermediate: alprazolam 0.5 mg, bromazepam 6 mg, clonazepam 2 mg; Low: alprazolam 0.25 mg; clorazepate 5-10 mg; diazepam 1-5 mg; lorazepam 1-2.5 mg; tetrazepam 50 mg.</p>
Rice <sup>37</sup> 2012 US (2007-2009)	Identify user characteristics and behaviour associated with diagnosed opioid abuse.	<p><b>Cohort</b> (N=821,916): aged 12-64 years; ≥1 opioid dispensings; continuously eligible in 12 months prior to index date. Cohort stratified by opioid abuse diagnosis. <b>A) Abusers</b> (N=6,380): ICD-9-CM code related to opioid</p>	<p><i>1) ≥1 early refills:</i> prescription opioid refill occurred with &gt;25% of the days' supply remaining on the previous prescription for the same active ingredient (12 months) <b>A) 38.4%</b> (n=2,449) <b>B) 4.1%</b> (n=33,343)</p>	<p><i>*Mean (SD) dispensing pharmacies (12 months)</i> <b>A) 2.4</b> (2.3) <b>B) 0.7</b> (0.9)</p> <p><i>*Mean (SD) prescribers (12 months)</i> <b>A) 3.2</b> (3.5) <b>B) 0.8</b> (1.3)</p> <p><i>*Mean (SD) prescriptions (12 months)</i> <b>A) 13.3</b> (13.1) <b>B) 1.9</b> (4.5)</p>	<p>*Abusers more likely to have filled opioid prescriptions previously (IR or ER). *Predictors of 'abusers': 1-5 prior opioid prescriptions (OR 2.23); 6 prior opioid prescriptions (OR 6.85); ≥1 prior prescription for buprenorphine (OR 51.75) or methadone (OR</p>

		dependence or poisoning in patient history <b>B) All other individuals</b> (N=815,536)		<p><i>*Mean (SD) opioids prescribed (12 months)</i> <b>A) 3.7 (3.7)</b> <b>B) 0.9 (1.4)</b></p> <p><i>*Mean (SD) active ingredients consumed in opioid prescriptions (12 months)</i> <b>A) 1.9 (1.3)</b> <b>B) 0.7 (0.9)</b></p> <p><i>*Prior use of propoxyphene (OR 0.73) or hydrocodone (OR 0.70) associated with a reduced probability of abuse when controlling for other factors.</i></p>	2.97); ≥1 diagnosis of non-opioid drug abuse (OR 9.89), mental illness (OR 2.45) or hepatitis (OR 2.36); family member diagnosis with opioid abuse (OR 3.01). <i>*The finding that abusers were more likely to receive prescriptions from multiple providers was not significant when controlling for other factors.</i>
Ross-Degnan <sup>38</sup> 2004 US (1988-1990)	Evaluate the impact of a triplicate prescription program (TPP) on problematic and non-problematic BZD use and on use of potential substitute	<b>Cohort:</b> ≥19 years; reside in New York or New Jersey; continuously enrolled in Medicaid for ≥10 out of 12 months for 1988-1990; ≥1 BZD dispensings. Excluded if: reside in nursing home for >1 month. <b>A) Baseline New York</b> (N=25,399) <b>B) Baseline New</b>	<p>1) <i>BZD treatment (&gt;120 days)</i> <b>A) 40.3% (n=10,236)</b> <b>C) 41.9% (n=4,579)</b> <b>B) 37.5% (n=10,073)</b> <b>D) 40.1% (n=10,793)</b></p> <p>2) <i>Excessive dose: average daily dose &gt;2 times MRDD (Various)</i> <b>A) 6.7% (n=1,702)</b> <b>C) 9.2% (n=1,006)</b> <b>B) 7.2% (n=1,934)</b> <b>D) 6.2% (n=1,669)</b></p> <p>3) <i>Concurrent use of 2 LA BZD in same class (120 days)</i> <b>A) 1.8% (n=458)</b> <b>C) 1.1% (n=121)</b> <b>B) 1.2% (n=323)</b> <b>D) 1.0% (n=270)</b></p>	<p><i>*Continuous use (&gt;330 days) and no seizure or panic diagnosis (Various)</i> <b>A) 16.2% (n=41,15)</b> <b>C) 15.7% (n=1,716)</b> <b>B) 13.7% (n=3,680)</b> <b>D) 16.9% (n=4,549)</b></p> <p><i>*Existence of any 'problematic' behaviour: outcome measures 1-6 and continuous use (&gt;330 days) and no seizure or panic diagnoses (Various)</i></p>	<p>*Pharmacy hopping greatly reduced in New York with a similar reduction for both potentially problematic and non-problematic BZD use. <i>*The TPP appears to have encouraged deliberate discontinuation of BZD therapy rather than reducing problems in</i></p>

	drugs.	<p><b>Jersey</b> (N=26,860)  <b>C) Post-TPP implementation New York</b> (N=10,928)  <b>D) Post-TPP New Jersey</b> (N=26,914):  TPP was not implemented in New Jersey.</p> <p>MRDD: 10 DME/day &gt;65 years; 20 DME/day for &lt;65 years.</p>	<p>4) <i>Concurrent use of 2 SA BZD in same class</i> (120 days )  <b>A) 3.7%</b> (n=940) <b>C) 2.5%</b> (n=274)  <b>B) 4.2%</b> (n=1,129) <b>D) 4.5%</b> (n=1,212)  5) <i>Receipt of ≥4 different BZDs</i> (120 days)  <b>A) 1.7%</b> (n=432) <b>C) 0.6%</b> (n=66)  <b>B) 1.9%</b> (n=511) <b>D) 1.9%</b> (n=512)  6) <i>Pharmacy hopping: dispensed same BZD from ≥2 pharmacies</i> (7 days)  <b>A) 7.7%</b> (n=1,956) <b>C) 3.7%</b> (n=405)  <b>B) 3.8%</b> (n=1,090) <b>D) 3.9%</b> (n=1,050)  7) <i>Receipt of a long half-life BZD for person aged &gt;65 years</i> (Various)  <b>A) 56.1%</b> (n unclear) <b>C) 51.3%</b> (n unclear)  <b>B) 52.6%</b> (n unclear) <b>D) 48.6%</b> (n unclear)</p>	<p><b>A) 42.8%</b> (n=10,871) <b>C) 45.1%</b> (n=4,929)  <b>B) 40.1%</b> (n=10,771) <b>D) 42.0%</b> (n=11,304)  *After TPP, there was a sudden and sustained reduction in BZD use in New York (-54.8%), with no changes in New Jersey.</p>	<p>use.  *More people in New York who used BZDs appropriately were affected by the policy, i.e. young AFDC women (Aid to Families with Dependent Children), living in low-income areas or high minority areas.</p>
Rouby <sup>39</sup> 2012 France (2005)	Assess the extent of tianeptine abuse compared to other antidepressants (ADs) and BZDs/Z-drugs.	<p><b>A) AD cohort</b> (N=410,525): ≥1 AD dispensings.  <b>B) BZD/Z-drug cohort</b> (N=663,107): ≥1 BZD/Z-drug dispensings.</p>	<p>1) <i>Doctor shopping quantity (DSQ):</i> amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months).  <i>Drug with highest DSQ:</i>  <b>A) Tianeptine:</b> 96,183 DDD  <b>B) Zolpidem:</b> 499,010 DDD  2) <i>Doctor shopping indicator (DSI):</i> proportion of total drug dispensed, obtained by DSQ (12 months). DSI ≥1% is a signal for abuse.  <i>Drug with highest DSI:</i></p>	<p>*<i>Volume of drug obtained via DSQ (DDD) (12 months)</i>  <b>A) Paroxetine:</b> 58,738  Fluoxetine: 52,383  Venlafaxine: 36,483  Mianserin: 15,344  Amitriptyline: 12,102  Mirtazapine: 10,285  Milnacipran: 4,417  <b>B) Flunitrazepam:</b> 436,647  Bromazepam: 379,785  Oxazepam: 109,239</p>	<p>*<i>Drugs with DSI≥1% (12 months)</i>  <b>A) Mianserin</b> 1.0%  <b>B) Clonazepam:</b> 3.0%  Zolpidem: 2.2%  Oxazepam: 2.1%  Diazepam: 2.0%  Bromazepam: 2.0%</p>

			<b>A) Tianeptine: 2.0%</b> <b>B) Flunitrazepam: 30.2%</b>	Clonazepam: 59,996 Diazepam: 47,339	
Seal <sup>40</sup> 2012 US (Oct 2005- Dec 2010)	Investigate the effect of mental health disorders on risk of adverse clinical outcomes associated with high use of prescription opioids.	<b>Cohort (N=141,209):</b> Iraq or Afghanistan veteran who entered VA database between Oct 2005-Dec 2008; within 12 months of entry received a non-cancer pain diagnosis (ICD-9-CM code); $\geq 1$ opioid dispensings for $\geq 20$ consecutive days. Stratified by mental health diagnosis (ICD-9-CM code). <b>A) No mental health diagnosis (n=4,488)</b> <b>B) Mental health diagnosis including PTSD (n=7,983)</b> <b>C) Mental health diagnosis excluding PTSD (n=3,205)</b> <b>D) Entire cohort (N=15,676): A) + B) + C)</b>	1) $\geq 1$ early refill: obtaining the same opioid prescription $>7$ days before the end of the previous prescription (12 months) <b>A) 20.4% (n=914)</b> <b>B) 33.8% (n=2,701)</b> <b>C) 30.6% (n=980)</b> <b>D) 29.3% (n=4,595)</b> 2) <i>Highest quintile for opioid dose</i> (12 months) <b>A) 15.9% (n=712)</b> <b>B) 22.7% (n=1,813)</b> <b>C) 19.2% (n=615)</b> <b>D) 20.0% (n=3,140)</b> 3) <i>Concurrent use of <math>\geq 2</math> types of opioids: <math>&gt;7</math> days of overlap (30 days)</i> <b>A) 10.7% (n=478)</b> <b>B) 19.8% (n=1,581)</b> <b>C) 17.3% (n=553)</b> <b>D) 16.7% (n=2,612)</b> 4) <i>Concurrent use of <math>\geq 2</math> types of sedative hypnotics: <math>&gt;7</math> days of overlap (30 days)</i> <b>A) 7.6% (n=343)</b> <b>B) 40.7% (n=3,251)</b> <b>C) 25.0% (n=802)</b> <b>D) 28.0% (n=4,396)</b> 5) <i>Median duration of opioid use <math>\geq 2</math></i>	*Adverse clinical outcomes for opioid users (12 months) i) <i>Opioid-related accidents and overdoses:</i> <b>A) 0.02% (n=1)</b> <b>B) 0.4% (n=29)</b> <b>C) 0.2% (n=7)</b> <b>D) 0.2% (n=37)</b> *Prevalence of all adverse clinical outcomes (wounding, alcohol injury, self-inflicted injury or violence) was greater for those prescribed an opioid. *Veterans with a mental health diagnosis were more likely to receive an opioid for pain than persons without a mental health diagnosis, and likelihood increased if the diagnosis included PTSD. *Veterans with PTSD were more likely to receive a sedative.	

			<p>months (12 months)</p> <p><b>A)</b> 42.7% (n=1,916)</p> <p><b>B)</b> 63.2% (n=5,047)</p> <p><b>C)</b> 57.0% (n=1,828)</p> <p><b>D)</b> 56.1% (n=8,791)</p>		
<p>Simoni-Wastila<sup>41</sup></p> <p>2004</p> <p>US</p> <p>(1988-1990, 1995)</p>	<p>Assess the effect of New York triplicate prescription program (TPP) on changes in BZD and other psychoactive drug use compared to New Jersey (no TPP).</p>	<p><b>A) New York</b> (N=6,054): reside in New York; ≥19 years; continuously enrolled in Medicaid for ≥10 out of 12 months for 1988-1990 and 1995; ≥1 inpatient or ≥2 outpatient diagnoses of a specified mood disorder in 1988.</p> <p><b>B) New Jersey</b> (N=6,875): A) but reside in New Jersey.</p>	<p>1) <i>Probably problematic behaviour:</i> dispensed same BZD from ≥2 pharmacies (7 days) OR BZD use &gt;2 times MRDD (time period not reported)</p> <p>Rate in 1988 to 1990 rates [% change]</p> <p><b>A)</b> 7.1 to 2.4 [-4.7%]</p> <p><b>B)</b> 4.0 to 3.4 [-0.6%]</p>	<p>*Probably non-problematic BZD use (BZD use of ≤120 days, no pharmacy hopping or high daily dose) was affected to a greater extent by TPP than problematic BZD use.</p> <p>*The implementation of the TPP resulted in abrupt, large and sustained reductions in BZD use among chronically ill users in New York relative to identically defined users in New Jersey who were not exposed to TPP.</p>	<p>*6 months post-TPP, anxiolytic use increased 85.7% in New York, sedative-hypnotic use increased 35.0%. There were no changes in utilisation for BZDs in New Jersey.</p> <p>*Reduction in BZD use was sustained 7 years after TPP.</p>
<p>Skurtveit<sup>42</sup></p> <p>2011</p> <p>Norway</p> <p>(2005-2008)</p>	<p>Determine prevalence of persistent/problematic opioid use.</p>	<p><b>A) Cohort</b> (N=245,006): ≥1 dispensings of a weak opioid (codeine, tramadol or dextropropoxyphene). Excluded if: received any opioid for palliative treatment of</p>	<p>1) <i>Persistent user:</i> dispensed ≥1 opioid (not further specified) each year from 2005 to 2008; in 2008 dispensed &gt;365 DDD of opioids in 2008 (48 months)</p> <p><b>A)</b> 0.3% (n=686)</p> <p>2) <i>Milder probable problematic user indicator:</i> dispensed ≥1 opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed &gt;365 DDD of</p>	<p>*9.5% of codeine users, 21.0% of tramadol users, and 22.3% of dextropropoxyphene users (in 2008) were dispensed a LA opioid as their first opioid in 2005.</p>	

		<p>malignant disease.</p> <p>Strong opioids: buprenorphine, fentanyl, hydromorphone, ketobemidone, morphine, oxycodone, pentazocine and pethidine.</p>	<p>opioids and <math>\geq 4</math> prescribers (48 months)</p> <p><b>A)</b> 0.2% (n=421)</p> <p>3) <i>Probable problematic user</i>: dispensed <math>\geq 1</math> opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed <math>&gt;365</math> DDD of opioids; <math>\geq 4</math> prescribers and <math>&gt;100</math> DDD of BZDs (48 months)</p> <p><b>A)</b> 0.08% (n=191)</p> <p>4) <i>Stricter probable problematic user indicator</i>: dispensed <math>\geq 1</math> opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed <math>&gt;365</math> DDD of opioids; <math>\geq 4</math> prescribers and <math>&gt;300</math> DDD of BZDs (48 months)</p> <p><b>A)</b> 0.06% (n=139)</p> <p>5) <i>Strictest probable problematic user indicator</i>: dispensed <math>\geq 1</math> opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed <math>&gt;365</math> DDD of opioids; <math>\geq 7</math> prescribers and <math>&gt;100</math> DDD of BZDs (48 months)</p> <p><b>A)</b> 0.05% (n=126)</p>		
Soumerai <sup>43</sup> 2003 US (1987-1990)	Determine if pharmacy hopping is associated with dose escalation in	<p><b>A) Entire cohort</b> (N=2,440): <math>\geq 2</math> years of BZD use; enrolled in Medicaid for <math>\geq 10</math> out of 12 months per year 1987-1990. (B + C)</p>	<p>1) <i>Pharmacy hoppers</i>: dispensed same BZD from <math>\geq 2</math> pharmacies (7 days)</p> <p><b>A)</b> 7.4% (n=180) <b>B)</b> 7.0% (n=139) <b>C)</b> 8.9% (n=41)</p> <p>2) <i>Users escalated to 'high' dosages</i>:</p>	*Predictors of dose escalation: <b>B+C)</b> regular use of SA, high potency BZD lorazepam; or young users (<45 years).	

	long term BZD users ( $\geq 2$ years) and identify predictors of dose escalation.	<b>B) Continuing BZD user</b> (N=1,980) A) but $\geq 2$ years of BZD use between 1988-1990. <b>C) Incident BZD user</b> (N=460): A) but no BZD use before Dec 1987.	20 (elderly patients) or 40 (younger patients) diazepam milligram equivalents per day (24 months) <b>A) 1.6%</b> (n=40) <b>B) 1.3%</b> (n=26) <b>C) 3.0%</b> (n=14)	<b>B) Use of antidepressants and pharmacy hopping</b> (OR 5.2). *Long-term use of BZDs is not associated with notable dose escalation.	
Sullivan <sup>44</sup> 2010 US (2000-2005)	Validate an indicator of opioid misuse and determine the demographic, clinical, and pharmacological risks associated with opioid misuse.	<b>A) Commercially insured</b> (N=21,685): $\geq 18$ years; chronic opioid user, i.e. $\geq 90$ days of opioid use in any 6 month period between Jan 2001-Dec 2004; continuous enrolment 12 months prior to and post index date (first opioid dispensing); identified in HealthCore dataset. Excluded if: $\geq 32$ day gap in opioid use; cancer diagnosis within 12 months of index date (pre- or post-); resident of nursing home or hospice user. <b>B) Publically insured</b>	1) <i>Opioid misuse score</i> : based on excess days supplied short- and long-acting opioids, number of dispensing pharmacies and prescribers (6 months). Score 0-1: no misuse <b>A) 70.0%</b> (n=15,180) <b>B) 76.0%</b> (n=7,721) Score 2-4: possible misuse <b>A) 24.0%</b> (n=5,205) <b>B) 20.0%</b> (n=2,032) Score $\geq 5$ : probable misuse <b>A) 6.0%</b> (n=1,302) <b>B) 3.0%</b> (n=305)	*For commercially insured cohort, risk of diagnosis of opioid abuse increased 41% for every 1 point increase in opioid misuse score. *For publically insured cohort, risk of diagnosis of opioid abuse increased 51% for every 1 point increase in opioid misuse score. *Factors that increase risk of opioid misuse: younger age, back pain, multiple pain complaints, substance abuse disorder, high daily dose of opioids ( $>120$ mg MED/day) and shorting acting schedule II opioids.	

		(N=10,159): A) but identified in Arkansas Medicaid.			
Thirion <sup>45</sup> 2002 France (Sep-Dec 1999)	Identify and profile deviant users dispensed buprenorphine (opioid).	<b>A) Cohort</b> (N=2,078): ≥1 buprenorphine dispensings.	1) <i>Deviant</i> : ≥3 prescribers or dispensed >20 mg/day of buprenorphine (4 months) <b>A)</b> 18.1% (n=377)	* <i>Number of prescribers</i> (4 months) 1 prescriber: 66% (n=1,371) 2 prescribers: 22% (n=457) 3-5 prescribers: 11% (n=229) ≥6 prescribers: 1% (n=21)	* <i>Deviant group profile</i> : younger, male and higher consumption of BZDs. * <i>Mean (SD) prescriptions</i> (4 months) Deviant user: 10.1 (5.9)
Victorri-Vigneau <sup>46</sup> 2006 France (second half of years 2001, 2002 and 2003)	Demonstrate impact of intervention program to reduce excessive doses of psychotropic drugs (drug class not further specified).	<b>A) Intervention cohort</b> (N=1,390) reside in Pays de Loire; dispensed >2 times maximum recommended daily dose (MRDD) for ≥3 consecutive months for one psychotropic drug. ( <i>Includes but is not limited to cohorts B and C.</i> ) <b>B) No action cohort</b> (N=422): A) and reimbursement code related to “serious problems of behaviour and personality”. <b>C) Action cohort</b>	Proportion of cohort pre-intervention to post-intervention 1) >2 <i>times MRDD</i> (3 consecutive months) <b>A)</b> 100% (n=1,390) to 89.5% (n=1,244) <b>B)</b> Figures not reported (reduction of 58.5% of patients meeting this criteria) <b>C)</b> Figures not reported (reduction of 66% of patients meeting this criteria) <b>D)</b> Figures not reported (reduction of 46.2% of patients meeting this criteria) 2) <i>Excess consumption</i> : average daily consumption exceeds MRDD specified in drug monograph (change from pre- to post-intervention) (12 months) <b>A)</b> Not reported <b>B)</b> 2.5 to 2.1 [-15%]	* <i>Mean number of prescribers</i> (12 months) [% change] <b>B)</b> Mean not reported [-4%] <b>C)</b> 2.67 to 2.28 [-15%] <b>D)</b> Mean not reported [2%] (direction of change not reported) * <i>R ratio</i> : number of patients receiving >2 MRDD of psychotropic drug to number of patients receiving psychotropic drug <b>C)</b> 100% (n=840) to 33.4% (n=281). *When considering all persons dispensed	*Health professionals involved with ‘action cohort’ filed 116 drug addiction reports. The prevalence of drugs mentioned in these reports: Zopiclone: 19% Zolpidem: 17% Oxazepam: 16% BZD (other): 13% Meprobamate: 11% Clorazepate: 9% Buprenorphine: 8% Bromazepam: 7%

		(N=840): <b>A</b> ); doctors and pharmacists of identified users received a letter to review their patients' medical prescriptions. Excluded if: assigned to <b>B</b> ); refusal to have data included in study; death, or moved residence. <b>D) Comparison cohort</b> (N not reported): <b>A</b> ) but reside in Vendee.	<b>C</b> ) 2.6 to 1.9 [-27%] <b>D</b> ) 2.3 to 2.1 [-9%]	psychotropic drug, the R ratio decreased by 14.1% over the study period.	
Victorri-Vigneau <sup>47</sup> 2011 France (Jul-Dec 2005)	Characterise AD over-consumption.	<b>A) Tianeptine</b> (N=7,264): ≥2 tianeptine dispensings. [MRDD = 37.5 mg] <b>B) Milnacipran</b> (N=1,918): ≥2 milnacipran dispensings. [MRDD = 100 mg]	1) <i>Overconsumer</i> : dispensed more drug than medically required (6 months) <b>A</b> ) Dispensed 1.7 times the MRDD: 0.4% (n=29) <b>B</b> ) Dispensed 2 times the MRDD: 2.4% (n=46) 2) <i>Pharmacy shoppers</i> : ≥4 dispensing pharmacies (6 months) • <i>In tianeptine overconsumers</i> (n=29): 20.7% (n=6) • <i>Other tianeptine users</i> (n=7,235): 1.0% (n=72) • <i>Milnacipran overconsumers</i> (n=46): 4.3% (n=2) • <i>Other milnacipran users</i> (n=1,872):	* <i>Median (range) prescribing physicians</i> (6 months) <b>A</b> ) 1 (1-6) <b>B</b> ) 1 (1-5) * <i>Median (range) dispensing pharmacies</i> (6 months) <b>A</b> ) 1 (1-13) <b>B</b> ) 1 (1-6) * <i>Median (range) dispensings</i> (6 months) <b>A</b> ) 5 (2-40) <b>B</b> ) 4 (2-17) * <i>Consumption factor &gt;1: estimate of average daily</i>	*The consumption factor reached higher values for tianeptine (up to 11 times higher) but occurred less frequently compared to milnacipran. *Pharmacy shopping increased risk of overconsumption for tianeptine (OR 10.78).

			<p>1.4% (n=26)</p> <p>3) % <i>R ratio</i>&gt;1: observed number of dispensings delivered to the user is greater than the amount actually required (6 months)</p> <ul style="list-style-type: none"> <li>• <i>Tianeptine overconsumers</i>: 89.7% (n=26)</li> <li>• <i>Other tianeptine user</i>: 27.9% (n=2,015)</li> <li>• <i>Milnacipran overconsumers</i>: 93.5% (n=43)</li> <li>• <i>Other milnacipran users</i>: 29.9% (n=560)</li> </ul>	<p>consumption of a psychotropic drug divided by the MRDD (6 months)</p> <p><b>A)</b> 17.2% (n=125)</p> <p><b>B)</b> 32.3% (n=620)</p>	
<p>Victorri-Vigneau<sup>48</sup></p> <p>2013</p> <p>France</p> <p>(Feb-Jul 2010)</p>	<p>Identify and characterise zolpidem and zopiclone (Z-drugs) users.</p>	<p><b>A) Zopiclone</b> (N=21,860): ≥1 zopiclone dispensings; number of dispensings are equal to or higher than medically required rate (3.75 mg).</p> <p><b>B) Zolpidem</b> (N=25,168): ≥1 zolpidem dispensings; number of dispensings are equal to or higher than medically required rate (5 mg).</p>	<p>1) <i>Problematic user</i>: latent class analysis based on: prescribing physician type, doctor shopping, pharmacy shopping, excess use, agreement with practice guidelines and associated psychiatric disorders (6 months)</p> <p><b>A)</b> 0% (n=0)</p> <p><b>B)</b> 1.0% (n=252)</p> <p>2) <i>Doctor shopper</i>: ≥4 prescribers (6 months)</p> <p><b>A)</b> 1.1% (n=241)</p> <ul style="list-style-type: none"> <li>• <i>In problematic zopiclone users</i>: 0% (n=0)</li> <li>• <i>In problematic zolpidem users</i>: 47.2% (n=119)</li> </ul>	<p>*<i>Problematic users mean (SD) daily dose (mg/day)</i> (6 months)</p> <p><b>A)</b> 0 (0)</p> <p><b>B)</b> 20.9 (2.4)</p> <p>*Zolpidem ‘problematic’ users were younger, average daily dose was higher and the number of dispensings is 2-fold higher.</p>	

			<p>3) <i>Pharmacy shopper</i>: <math>\geq 4</math> dispensing pharmacies (6 months)  <b>A) 1.7%</b> (n=372)  • <i>In problematic zopiclone users</i>: 0% (n=0)  <b>B) 2.1%</b> (n=529)  • <i>In problematic zolpidem users</i>: 84.1% (n=212)  4) <i>Excess use</i>: medication possession ratio (MPR) <math>&gt;1</math>: number of drug supply days excluding last refill divided by the number of days between the first and last dispensing (6 months)  <b>A) 32.8%</b> (n=7,171)  • <i>In problematic zopiclone users</i>: 0% (n=0)  <b>B) 31.2%</b> (n=7,853)  • <i>In problematic zolpidem users</i>: 75.0% (n=189)</p>		
Wainstein <sup>49</sup> 2011 France (Jan-Jun 2008)	Characterise consumption behaviour related to three psychotropic drugs (BZD, Z-drugs and AD).	<p><b>A) Bromazepam</b> (N=40,644): <math>\geq 18</math> years; <math>\geq 2</math> bromazepam dispensings. [MRDD = 18 mg].  <b>B) Zolpidem</b> (N=36,264) <math>\geq 18</math> years; <math>\geq 2</math> zolpidem dispensings. [MRDD = 10 mg].  <b>C) Paroxetine</b></p>	<p>1) <i>Problematic user</i>: latent class analysis based on excessive drug use, prescribing physician specialty, 'doctor shopping' behaviour, 'pharmacy shopping' behaviour, prescription in agreement with practice guidelines (6 months)  <b>A) 1.0%</b> (n=407)  <b>B) 1.0%</b> (n=363)  <b>C) 0%</b> (n=0)  2) <i>Pharmacy shoppers</i>: <math>\geq 4</math> dispensing</p>		

		<p>(N=31,235): ≥18 years;  ≥2 paroxetine dispensings.  [MRDD = 40 mg].</p> <p>Excluded if: 2 dispensings received on the same day.</p>	<p>pharmacies (6 months)</p> <p><b>A)</b> 1.2% (n=488)</p> <ul style="list-style-type: none"> <li>• <i>In problematic bromazepam users:</i> 93.1% (n=379)</li> </ul> <p><b>B)</b> Not reported</p> <ul style="list-style-type: none"> <li>• <i>In problematic zolpidem users:</i> 65.0% (inferred from graph) (n=236)</li> </ul> <p><b>C)</b> Not reported</p> <ul style="list-style-type: none"> <li>• <i>In problematic paroxetine users:</i> 0%</li> </ul> <p>3) <i>Doctor shoppers: ≥4 prescribers doctors (6 months)</i></p> <p><b>A)</b> 0.4% (n=163)</p> <ul style="list-style-type: none"> <li>• <i>In problematic bromazepam users:</i> 41.0% (n=167)</li> </ul> <p><b>B)</b> Not reported</p> <ul style="list-style-type: none"> <li>• <i>In problematic zolpidem users:</i> 32% (inferred from graph) (n=117)</li> </ul> <p><b>C)</b> Not reported</p> <ul style="list-style-type: none"> <li>• <i>In problematic paroxetine users:</i> 0%</li> </ul> <p>4) <i>Estimate of average daily consumption of a psychotropic drug greater than MRDD (6 months)</i></p> <p><b>A)</b> 1.1% (n=448)</p> <ul style="list-style-type: none"> <li>• <i>In problematic bromazepam users:</i> 56.0% (n=228)</li> </ul> <p><b>B)</b> 17.8% (n=6,455)</p> <ul style="list-style-type: none"> <li>• <i>In problematic zolpidem users:</i> 89.0% (inferred from graph) (n=324)</li> </ul> <p><b>C)</b> 0.3% (n=94)</p> <ul style="list-style-type: none"> <li>• <i>In problematic paroxetine users:</i> 0%</li> </ul>		
--	--	--	--	--	--

			(n=0)		
White <sup>50</sup> 2009 US (2005-2006)	Assess feasibility of using medical and prescription drug claims to develop models that identify prescription opioid abuse or misuse.	<p>Model A cohort details.</p> <p><b>A) Cohort</b> (N=116,382): aged 12-64, ≥1 opioid claim and ≥1 medical claim. (B + C)</p> <p><b>B) Abusers</b> (N=875): A) ICD-9-CM code of opioid dependence or poisoning. <b>C) All other individuals</b> (N=115,507): A) not B)</p> <p>Model B cohort details</p> <p><b>D) Cohort (subset of A)</b> (N=8,592): A) claims occurred Sep-Dec 2006. (E + F)</p> <p><b>E) Abusers</b> (N=303): B) between Sep-Dec 2006. <b>F) All other individuals</b> (N=8,289): C) not E).</p>	<p>1) <i>Number of prescribers</i>: ≥2 prescribers (3 months)  <b>A)</b> not analysed: <b>D)</b> 26.1% (n=2,242)  <b>B)</b> not analysed: <b>E)</b> 40.9% (n=124)  <b>C)</b> not analysed: <b>F)</b> 25.6% (n=2,118)</p> <p>2) <i>Pharmacy shopper</i>: ≥2 dispensing pharmacies (3 months)  <b>A)</b> 7.9% (n=9,213): <b>D)</b> 19.9% (n=1,708)  <b>B)</b> 39.4% (n=345): <b>E)</b> 38.0% (n=115)  <b>C)</b> 7.7% (n=8,868): <b>F)</b> 19.2% (n=1,593)</p> <p>3) <i>≥4 opioid prescriptions</i> (3 months)  <b>A)</b> 10.1% (n=11,740): <b>D)</b> not analysed  <b>B)</b> 60.1% (n=526): <b>E)</b> not analysed  <b>C)</b> 9.7% (n=11,214): <b>F)</b> not analysed</p> <p>4) <i>≥1 early refills of opioid prescriptions</i>: two consecutive opioid prescriptions where days of supply of first prescription was &gt;10% higher than the number of days between prescriptions (3 months)  <b>A)</b> 4.0% (n=4,615): <b>D)</b> 16.5% (n=1,414)  <b>B)</b> 36.0% (n=315): <b>E)</b> 40.9% (n=124)  <b>C)</b> 3.7% (n=4,300): <b>F)</b> 15.6% (n=1,290)</p> <p>5) <i>Dose escalation</i>: 50% increase in the mean milligrams of morphine per month for 2 consecutive months (3 months)  <b>A)</b> 0.4% (n=509): <b>D)</b> not analysed  <b>B)</b> 4.7% (n=41): <b>E)</b> not analysed</p>	*Factors associated with ICD-9-CM code of opioid abuse, dependence or poisoning (not related to an outcome measure defining misuse): male (OR 2.19), ≥3 dispensing pharmacies (OR 1.96), ≥1 early refills of opioid prescriptions (OR 6.52), ≥2 consecutive months of dose escalation (OR 1.59), ≥12 opioid prescriptions (OR 2.12), ≥1 non-opioid substance abuse diagnosis (OR 5.83).	

			<b>C) 0.4% (n=468): F) not analysed</b>		
Wilsey <sup>51</sup> 2010 US (2007)	Determine prevalence and predictors of multiple provider episodes (MPEs) for different controlled substances.	<b>A) Cohort</b> (N not reported): prescription for schedule II-IV controlled substances. Excluded if: missing or incomplete user or provider identification; implausible prescriptions; use of drugs not suggestive of standard delivery systems employed by most users. Prescription level data (N=27,773,347)	1) <i>Prescriptions obtained by multiple provider episodes (MPEs):</i> ≥2 prescribers and ≥2 dispensing pharmacies (30 days) <b>A) 8.4%</b> (n prescriptions=2,332,962) 2) <i>Proportion of prescription obtained by MPEs by drug class:</i> Opioids: 12.8% BZDs: 4.2% Stimulants: 1.4% Anorectics: 0.9%	<i>*Risk of simultaneous MPEs for different controlled substances:</i> <i>i) Opioids and:</i> BZD: OR 15.54 Stimulants/anorectics: OR 10.56 BZD and stimulants/anorectics: OR 21.40 <i>ii) BZD and:</i> Opioids: OR 13.04 Stimulants/anorectics: OR 20.60 Stimulants/anorectics and opioids: OR 3.64 <i>iii) Stimulant and:</i> BZD: OR 19.62 Opioids: OR 9.23 BZD and opioids: OR 26.83 <i>iv) Anorectic and:</i> BZD: OR 9.95 Opioids: OR 11.06 BZD and opioids: OR 27.16	<i>*For opioids: hydromorphone and controlled release oxycodone were most associated with MPEs. *Younger age predictor of MPEs associated with opioid and BZDs. *Older age associated with MPE use to obtain stimulants and anorectics. *Males were more likely to use MPE for BZD; less likely for stimulants; no gender relationship between anorectics or opioids. *Strongest predictor was simultaneously receiving prescriptions for different controlled substances and concurrent use of multiple prescribers to obtain other controlled substances.</i>
Wilsey <sup>52</sup> 2011	Determine if persons	<b>A) Cohort</b> (N=12,870,831)	1) <i>Multiple prescribers:</i> 2-5 prescribers (12 months)	<i>*Single prescriber</i> (12 months)	<i>*Persons accessing 2-5 prescribers are different</i>

US (1999-2007)	accessing 2-5 prescribers were distinguishable from persons accessing one prescriber in demographic characteristics or opioid utilisation (opioid).	Prescribed same schedule II or III opioid in 12 months. Excluded if: missing/incomplete prescription, pharmacy or prescriber information; implausible prescription; use of opioids not suggestive of chronic pain.	<b>A) 22.1%</b> (n=2,849,464) 2) <i>Frequency of use of multiple prescribers per drug</i> (12 months) Hydrocodone (schedule III): 68.3% Codeine (schedule III): 9.8% Oxycodone IR (schedule II): 7.8% Oxycodone ER (schedule II): 3.0% Fentanyl (transcutaneous) (schedule II): 4.0% Morphine ER (schedule II): 3.2% Methadone (schedule II): 1.5% Hydromorphone (schedule II): 1.5% Morphine IR (schedule II): 0.6% Fentanyl (oral transbuccal): 0.1% Meperidine (schedule II): 0.1% Levorphanol (schedule II): 0.02%	<b>A) 77.9%</b> (n=10,021,367) *Persons accessing 2-5 prescribers were more likely to use LA opioids than hydrocodone (ranging from 7.8% [fentanyl patch] to 38.8% [methadone]) and less likely to use SA opioids. *Likelihood of MPEs increased with age. *Persons with multiple prescribers were more likely to: be female; reside in a small geographic area.	from those using one prescriber, but differences do not suggest abuse.
----------------	---	--	---	---	--

<sup>a</sup> See Electronic Supplementary Material 6 for reference list.

<sup>b</sup>Period of observation covers the entire year, unless otherwise stated.

<sup>c</sup>Reported aim(s) and cohort(s) may differ from original article as we only report aspects of paper related to prescription drug misuse.

<sup>d</sup>We renamed/redefined some measures from the original manuscript for clarity and due to space constraints. If either a rate or the number of people identified by a measure was not reported, where possible we calculated it. All reported rates were derived from drug-user or misuse cohorts unless otherwise stated.

**ACRONYMS:**

AD(s): antidepressant(s)

AP: antiparkinson

BMT: buprenorphine maintenance therapy

BZD(s): benzodiazepine(s)

DDD: defined daily dose

DSI: doctor shopping indicator

DSQ: doctor shopping quantity  
DME: diazepam milligram equivalent  
ED: emergency department  
ER: extended release  
GP(s): general practitioner(s)  
HDB: high dosage buprenorphine  
ICD: International Classification of Diseases  
IR: immediate release  
LA: long-acting  
MPE(s): multiple provider/prescriber episode(s)  
MRDD: maximum recommended daily dose  
OMT: opioid maintenance therapy  
OR: odds ratio  
PMP: prescription monitoring program  
PTSD: Post-Traumatic Stress Disorder  
SA: short-acting

## Supplementary Material 2.8 The reported extent of prescription drug misuse based on indicators

with a defined threshold

### Supplementary Material 2.8.1 Proportion of cohort identified as 'misusers' based on indicators with a defined threshold

#### A. Stand-alone measures of misuse (drug-users only)

<b>Stand-alone measure details</b> (A single behaviour of misuse measured in drug-users: persons dispensed the drug of interest)	<b>Time period (days)<sup>a</sup></b>	<b>Drug-user cohort<sup>b</sup></b>	<b>Reference<sup>c</sup></b>
<b>Number of prescribers</b>			
≥2 prescribers	90	26.1	50
2-5 prescribers	365	22.1	52
≥3 prescribers	365	NM	16
≥4 prescribers	180	0.9	2
≥4 prescribers	NR	0.5	3
≥4 prescribers	180	3.6	33
≥4 prescribers	180	1.1	48
≥4 prescribers	180	0.4	49
<b>Number of dispensing pharmacies</b>			
≥2 dispensing pharmacies	7	1.9	32
≥2 dispensing pharmacies	7	3.9	38
≥2 dispensing pharmacies	7	8.9	43
≥2 dispensing pharmacies	90	19.9	50
≥4 dispensing pharmacies	180	1.3	2
≥4 dispensing pharmacies	180	1.3	33
≥4 dispensing pharmacies	180	1.4	47
≥4 dispensing pharmacies	180	2.1	48
≥4 dispensing pharmacies	180	1.2	49
<b>Volume of drug dispensed</b>			
≥1 benzodiazepine dispensings per year for 4 consecutive years	1440	2.2	20
≥4 dispensings	90	10.1	50
>15 defined daily doses of carisoprodol	365	32.2	3
≥100 defined daily doses of opioids	365	13.6	3
>365 defined daily doses of codeine	365	5.8	14
>1000 defined daily doses of carisoprodol	365	0.2	4
Daily dose ≥100 morphine milligram equivalent	365	7.8	23
Daily consumption of drug greater than maximum recommended daily dose	180	17.8	49
>2 times maximum recommended dose	Various	9.2	38
≥2 times maximum daily dose	180	2.4	47
Number of dispensings greater than medically required	180	29.9	47
<b>Overlapping prescriptions or early refills</b>			
≥1 early refills: two consecutive prescriptions for same drug	365	6.9	22

with number of days between prescriptions being >10% lower than number of days' supply in first prescription			
1 early refill: prescription filled >7 days before the end of previous prescription	365	33.8	40
≥1 early refills: two consecutive opioid prescriptions where days of supply was >10% higher than number of days between prescriptions	90	16.5	50
≥1 early refills: prescription opioid refill that occurred with >25% of the days' supply remaining on the previous prescription for the same active ingredient	365	4.1	37
≥4 days of overlapping prescriptions	540	11.1	5
≥7 days of overlapping prescriptions	365	2.1	23
<b>Use of specific prescribed drug</b>			
Long-acting or extended release opioids prescribed for acute pain conditions	365	0.1	23
Use of ≥4 different benzodiazepines	Various	1.9	38
Receipt of long half-life benzodiazepines (persons aged ≥65 years)	NR	51.3	38
<b>Duration of treatment</b>			
Median duration of opioid use ≥2 months	365	63.2	40
>120 days of benzodiazepine treatment	Various	41.9	38
<b>Dose escalation</b>			
Users escalating to 'high' dosages: 20 (elderly patients) or 40 (younger patients) diazepam milligram equivalents per day	NR	3.0	43
50% increase in mean milligrams of morphine per month for 2 consecutive months	90	0.4	50

<sup>a</sup> All time periods have been converted to days, i.e. 30 days = 1 month; 90 days = 3 months; 180 days = 6 months; 365 days = 12 months etc. NR = not recorded in original manuscript.

<sup>b</sup> If study reported rates for >1 drug-user cohort or drug, we record the highest reported rate alone.

<sup>c</sup> See Electronic Supplementary Material 6 for reference list.

NM = no meaningful result was obtained.

NR = not recorded in original manuscript.

B. Composite measures: a single measure of misuse reported in a misuse cohort (where possible, we also record the extent of misuse in the drug-user cohort)

<b>Composite measure of misuse details</b> (A single behaviour of misuse measured in a defined misuse cohort) <i>Misuse cohort definition</i>	<b>Time period (days)<sup>a</sup></b>	<b>Drug-user cohort<sup>b</sup></b>	<b>Misuse cohort<sup>b</sup></b>	<b>Reference<sup>c</sup></b>
<b>Number of prescribers</b>				
≥2 prescribers <i>Misuse cohort definition: ICD-9 code of opioid abuse, dependence or poisoning</i>	90	26.1	40.9	50
≥3 prescribers ≥1 days of overlapping prescriptions	540	(0.7)	5.4	5
≥4 prescribers 2 defined daily doses (DDD)/day of carisoprodol;	NR	0.6	4.5	3

<i>dispensed &lt;100 DDD of opioids, and dispensed &lt;100 DDD of benzodiazepines in 365 days</i>				
≥4 prescribers <i>Drug-related death</i>	180	3.6	25.2	33
≥4 prescribers <i>≥4 dispensing pharmacies</i>	180	(0.7)	55.6	33
≥4 prescribers <i>Highest 1% zolpidem users determined by latent class analysis</i>	180	(0.5)	47.2	48
≥4 prescribers <i>Highest 1% bromazepam users determined by latent class analysis</i>	180	(0.4)	41.0	49
≥5 prescribers <i>Pharmaceutical overdose death</i>	365	N/A	21.4	18
<b>Number of dispensing pharmacies</b>				
≥2 dispensing pharmacies <i>Misuse cohort definition: ≥1 days of overlapping prescriptions</i>	540	(2.8)	21.3	5
≥2 dispensing pharmacies <i>ICD-9 code of opioid abuse, dependence or poisoning</i>	90	19.9	39.4	50
≥3 dispensing pharmacies <i>≥1 days of overlapping prescriptions</i>	540	(0.2)	1.3	5
≥4 dispensing pharmacies <i>Drug-related death</i>	180	1.3	17.5	33
≥4 dispensing pharmacies <i>≥4 prescribers</i>	180	(0.7)	20.2	33
≥4 dispensing pharmacies <i>Dispensed 1.7 or 2 times more drug than medically required</i>	180	1.4	20.7	47
≥4 dispensing pharmacies <i>Highest 1% zolpidem users determined by latent class analysis</i>	180	(0.8)	84.1	48
≥4 dispensing pharmacies <i>Highest 1% bromazepam users determined by latent class analysis</i>	180	(0.9)	93.1	49
<b>Volume of drug dispensed</b>				
>2 times maximum recommended daily dose (post-intervention) <i>Misuse cohort definition: Pre-intervention dispensed &gt;2 times maximum recommended daily dose</i>	90	N/A	89.5	46
≥4 prescriptions <i>ICD-9 code of opioid abuse, dependence or poisoning</i>	90	10.1	60.1	50
>15 defined daily dose (DDD) of carisoprodol <i>&gt;365 DDD of codeine</i>	365	(1.7)	30.2	14

≥16 mg per day of high dosage buprenorphine ≥2 overlapping prescriptions and ≥2 prescribers	480	(3.4)	8.5	34
>100 defined daily dose (DDD) of benzodiazepines <i>Dispensed &gt;365 DDD of codeine</i>	365	(2.9)	50.5	14
>730 defined daily dose (DDD) of codeine <i>Dispensed &gt;365 DDD of codeine</i>	365	(1.1)	19.0	14
Medication possession ratio >1: number of drug supply days excluding last refill divided by the number of days between the first and last dispensing. <i>Number of dispensings greater than medically required</i>	180	N/A	32.8	48
Number of dispensings greater than medically required <i>Dispensed 1.7 or 2 times more drug than medically required</i>	180	29.9	93.5	47
Amount of drug dispensed greater than medically required <i>Highest 1% zolpidem users determined by latent class analysis</i>	180	(0.8)	75.0	48
Daily consumption of drug greater than medically required <i>Highest 1% zolpidem users determined by latent class analysis</i>	180	(0.9)	89.0	49
<b>Overlapping prescriptions or early refills</b>				
≥1 early refills: two consecutive opioid prescriptions where days of supply was >10% higher than number of days between prescriptions <i>Misuse cohort definition: ICD-9 code of opioid dependence or poisoning</i>	90	16.5	40.9	50
≥1 early refills: any prescription opioid refill that occurred with >25% of the days' supply remaining on the previous prescription for the same active ingredient <i>ICD-9 code of opioid dependence or poisoning</i>	365	4.1	38.4	37
<b>Dose escalation</b>				
50% increase in the mean milligrams of morphine in 2 consecutive months <i>Misuse cohort definition: ICD-9 code of opioid dependence or poisoning</i>	90	0.4	4.7	50

<sup>a</sup> All time periods have been converted to days, i.e. 30 days = 1 month; 90 days = 3 months; 180 days = 6 months; 365 days = 12 months etc. N/A = not applicable as study investigated measure in misuse cohort alone

<sup>b</sup> Where studies report multiple results across drug or user cohorts we record the highest reported rate. We calculated all bracketed and italicised values. Values were not reported in original manuscript.

<sup>c</sup> See Electronic Supplementary Material 6 for reference list.

C. Composite measures: measure of misuse with two or more behaviours or characteristics reported in drug-user and/or misuse cohort(s)

<b>Composite measure details</b> (≥2 behaviours/characteristics of misuse measured in drug-user and/or misuse cohorts) <i>Misuse cohort definition (where applicable)</i>	<b>Time period (days)<sup>a</sup></b>	<b>Drug-user cohort<sup>b</sup></b>	<b>Misuse cohort<sup>b</sup></b>	<b>Reference<sup>c</sup></b>
<b>Composite measures of misuse including number of prescribers and/or number of dispensing pharmacies</b>				
≥2 prescribers and ≥1 days overlapping prescriptions	540	13.9		5
≥2 prescribers and ≥1 days overlapping prescriptions	480	39.5		34
≥2 dispensing pharmacies in 7 days or benzodiazepine treatment duration >120 days or dispensed >2 times maximum recommended daily dose	Various	42.8		32
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	540	NR		6
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	365	0.9		8
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	540	0.7		9
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	540	0.3		7
≥2 dispensing pharmacies within 7 days OR dispensed >2 times maximum recommended daily dose	Various	3.4		41
≥3 dispensing pharmacies and ≥1 overlapping prescriptions	540	0.2		5
≥3 prescribers and ≥3 dispensing pharmacies	365	1.6		22
≥3 prescribers or dispensed >20 mg/day of buprenorphine	120	18.1		45
≥4 prescribers and ≥4 dispensing pharmacies	365	0.5		22
≥4 prescribers, ≥1 opioid dispensings for 4 consecutive years and in final year dispensed >365 defined daily doses of opioids	1460	0.2		42
≥4 prescribers, ≥1 opioid dispensings for 4 consecutive years, in final year dispensed >365 defined daily doses (DDD) of opioids and >100 DDDs of benzodiazepines	1460	0.08		42
≥4 prescribers, ≥1 opioid dispensings for 4 consecutive years, in final year dispensed >365 defined daily doses (DDD) of opioids and >300 DDD of benzodiazepines	1460	0.06		42
≥5 prescribers and ≥5 dispensing pharmacies	365	0.2		22
≥5 shopping episodes: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions (1	365	0.07		8

shopping episode)				
≥5 shopping episodes: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions (1 shopping episode)	540	0.1		9
≥6 shopping episodes: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions (1 shopping episode) <i>Misuse cohort definition: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions</i>	540	(0.03)	9.5	7
≥7 prescribers, ≥1 opioid dispensings for 4 consecutive years, in final year dispensed >365 defined daily doses (DDD) of opioids and >100 DDD of benzodiazepines	1460	0.05		42
Opioid misuse score: possible misuse score (score 2-3): based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	14.5		25
Opioid misuse score: possible or probable misuse score (score 2-4). Score based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	24.0		44
Opioid misuse score: probable misuse score (score ≥4) Score based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	2.2		25
Opioid misuse score: probable misuse score (score ≥5) Score based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	6.0		44
≥2 letters sent out to physician informing them of patient's problematic use of prescribed drug. Based on alerts of number of prescribers or dispensing pharmacies and/or amount of drug prescribed. <i>Physician previously sent a letter describing patient's problematic use of prescription drug(s)</i>	180	N/A	29.8	21
<b>Composite measures of misuse including volume of drug dispensed:</b> none of the listed measures below include number of prescribers or dispensing pharmacies.				
≥1 opioid dispensings for 4 consecutive years; and in final year dispensed >365 defined daily doses of opioids	1460	0.3		42
2 defined daily doses (DDD) per day of carisoprodol, <100 DDD of benzodiazepines and <100 DDD of opioids	365	1.0		3
≥100 defined daily doses (DDD) of benzodiazepines	365	7.8		3

and <100 DDD of opioids				
≥2 dispensings of carisoprodol and dispensed: >15 defined daily doses (DDD) of carisoprodol, >2 times recommended maximum daily dose for a period, <100 DDD of opioids and <100 DDD of benzodiazepines	365	1.0		4
Dispensed ≥100 defined daily doses (DDD) of benzodiazepines and/or ≥15 DDD of carisoprodol	365	50.1		1
Dispensed ≥100 defined daily doses (DDD) of benzodiazepines or ≥15 DDD of carisoprodol	365	41.9		1
Dispensed ≥100 defined daily doses (DDD) of benzodiazepines and ≥15 DDD of carisoprodol	365	8.2		1
Dispensed >2 times maximum recommended daily dose or benzodiazepine treatment duration >120 days	Various	40.2		32
<b>Composite measures of misuse including early refills or overlapping prescriptions:</b> none of the measures listed below include number of prescribers, dispensing pharmacies or volume of drug dispensed				
Opioid and BZD prescription with ≥7 days overlap	365	1.0		23
Concurrent use of 2 long-acting benzodiazepines	Various	1.1		38
Concurrent use of 2 short-acting benzodiazepines	Various	4.5		38
≥2 types of concurrent opioid use with >7 days overlap	30	19.8		40
≥2 types of concurrent sedative hypnotic use	30	40.7		40

<sup>a</sup> All time periods have been converted to days, i.e. 30 days = 1 month; 90 days = 3 months; 180 days = 6 months; 365 days = 12 months etc. N/A = not applicable as study investigated measure in misuse cohort alone. NR = not recorded in original manuscript.

<sup>b</sup> Where studies report multiple results across drug or user cohorts we record the highest reported rate. We calculated all bracketed and italicised values. Values were not reported in original manuscript.

<sup>c</sup> See Electronic Supplementary Material 6 for reference list.

*Electronic Supplementary Material 2.8. Proportion of misusers determined through empirical analysis.*

<b>Empirical analysis details (empirically derived thresholds of misuse where relevant)</b>	<b>Time period (days)<sup>a</sup></b>	<b>Drug-user cohort<sup>b</sup></b>	<b>Reference<sup>c</sup></b>
Excessive use based on Peaks Over Threshold model	180	7.2	2
Highest 1% of carisoprodol users based on Lorenz curve (dispensed ≥480 defined daily doses)	365	1.1	4
Highest 10% of codeine users (≥120 defined daily doses)	365	10.7	1
Highest quintile (20%) of opioid users	365	22.7	40
Cluster analysis based on number of: prescribers; dispensing pharmacies; dispensing episodes and sum of DDD dispensed	270	1.1	12
Cluster analysis based on number of: prescribers; dispensing pharmacies; dispensing episodes and sum of DDD dispensed	270	1.1	13
Cluster analysis based on number of: prescribers; dispensing pharmacies; dispensing episodes and sum of DDD dispensed	270	6.0	29

Cluster analysis based on number of: prescribers; dispensing pharmacies; dispensing episodes and sum of DDD dispensed	270	9.1	30
Latent class analysis based on gender; age and method of payment	300	0.7	26
Highest 1% of drug-users based on latent class analysis including consumption factor; prescriber specialty; number of prescribers; number of dispensing pharmacies; consistent with practice guidelines	180	1.0	49
Highest 1% of drug-users based on latent class analysis including prescriber specialty; number of prescribers; number of dispensing pharmacies; excess use; consistent with practice guidelines; associated psychiatric disorders	180	1.0	48

<sup>a</sup> All time periods have been converted to days, i.e. 180 days = 6 months; 365 days = 12 months etc.

<sup>b</sup> Where studies report multiple results across drug or user cohorts we record the highest reported rate.

<sup>c</sup> See Electronic Supplementary Material 6 for reference list.

**Supplementary Material 2.9** The proportion of prescription drugs dispensed to a misuse cohort: determined by a measure of misuse with a defined threshold

A. Stand-alone and composite measures of misuse reporting the proportion of drugs dispensed to misuser cohorts

<b>Drug class of interest</b> <i>(Misuse cohort definition)</i>	<b>Time period (days)<sup>a</sup></b>	<b>Proportion of drug class dispensed to a misuse cohort</b>	<b>Reference<sup>b</sup></b>
Anorectics <i>Misuser cohort definition: ≥2 prescribers and ≥2 dispensing pharmacies</i>	30	0.9	51
Benzodiazepines <i>≥2 prescribers and ≥2 dispensing pharmacies</i>	7	1.2	10
Benzodiazepines <i>≥2 prescribers and ≥2 dispensing pharmacies</i>	30	4.2	51
Opioids <i>≥2 prescribers and ≥2 dispensing pharmacies</i>	7	3.2	10
Opioids <i>≥2 prescribers and ≥2 dispensing pharmacies</i>	30	9.6	15
Opioids <i>≥2 prescribers and ≥2 dispensing pharmacies</i>	30	12.8	51
Opioids <i>≥3 prescribers and ≥3 dispensing pharmacies</i>	365	7.7	22
Opioids <i>≥4 prescribers and ≥4 dispensing pharmacies</i>	365	3.1	22
Opioids <i>≥5 prescribers and ≥5 dispensing pharmacies</i>	365	1.5	22
Stimulants <i>≥2 prescribers and ≥2 dispensing pharmacies</i>	30	1.4	51
<b>Prescription drug of interest</b> <i>(Misuse cohort definition)</i>	<b>Time period (days)<sup>a</sup></b>	<b>Proportion of drug dispensed to a misuse cohort<sup>c</sup></b>	<b>Reference<sup>b</sup></b>
Buprenorphine <i>Misuse cohort definition: Doctor shopping quantity: amount of excess drug obtained by misusers by overlapping prescriptions from ≥2 prescribers</i>	485	18.7	34
Hydrocodone <i>≥2 prescribers</i>	365	68.3	52
Hydromorphone <i>≥2 prescribers and ≥2 dispensing pharmacies</i>	30	15.2	15

<sup>a</sup> All time periods have been converted to days, i.e. 30 days = 1 month; 365 days = 12 months etc.

<sup>b</sup> See Electronic Supplementary Material 6 for reference list.

<sup>c</sup> Per drug class, we report the result of the drug with the highest DSI.

B. Composite measures of misuse reporting the volume of drugs dispensed to misuse cohorts: specific measures of doctor shopping quantity (DSQ) and doctor shopping indicator (DSI)

Drug class or drug of interest	Time period (days) <sup>a</sup>	Measure of misuse: DSQ <sup>b</sup>	Measure of misuse: DSI (%) <sup>b</sup>	Reference <sup>c</sup>
<b>Doctor shopping quantity (DSQ):</b> amount of excess drug obtained by misusers by overlapping prescriptions from $\geq 2$ prescribers				
<b>Doctor shopping indicator (DSI) (%):</b> amount of drug calculated by the DSQ, expressed as the proportion of total drug dispensed (i.e. DSQ/total drug volume dispensed). DSI >1% is a signal for drug abuse.				
<i>Drug class</i>				
Benzodiazepines	NR	<sup>d</sup>	1.9	31
Benzodiazepines	365	361,428 DDD	NR	36
Opioids (opioid maintenance therapy)	365	55.3 DDD/1000 population	6.2	27
<i>Antidepressants</i>				
Mianserin	365	15,344 DDD	1.0	39
<i>Benzodiazepine</i>				
Flunitrazepam	365	<sup>d</sup>	27.0	30
Flunitrazepam	365	108,727 DDD	42.8	36
Flunitrazepam	365	436,647 DDD	30.2	39
<i>Opioids</i>				
Buprenorphine	365	1151 grams	21.7	35
Buprenorphine (opioid maintenance therapy)	365	50.3 DDD/1000 population	8.0	27
Buprenorphine (opioid maintenance therapy)	NR	<sup>d</sup>	12.5	31
<i>Z-drugs</i>				
Zolpidem	365	<sup>d</sup>	2.5	30
Zolpidem	365	499,010 DDD	2.2	39

<sup>a</sup> All time periods have been converted to days, i.e. 365 days = 12 months etc. NR = not recorded in original manuscript.

<sup>b</sup> Per drug class, we report the result of the drug with the highest DSI.

<sup>c</sup> See Electronic Supplementary Material 6 for reference list.

<sup>d</sup> DSQ not investigated in study

C. Proportion of drug dispensed to empirically defined misuse cohort

<b>Empirical analysis details</b>	<b>Time period (days)<sup>a</sup></b>	<b>Proportion of drug of interest dispensed to misuse cohort<sup>b</sup></b>	<b>Reference<sup>c</sup></b>
Highest 1% of benzodiazepine drug-users based on Lorenz curve	365	16.5	16
Highest 1% of carisoprodol users	365	18.7	4
Highest 1% of biperiden drug-users based on Lorenz curve	365	6.2	16

<sup>a</sup> All time periods have been converted to days, i.e. 365 days = 12 months etc.

<sup>b</sup> Where studies report multiple results relating to one drug class we report the drug with the highest rate.

<sup>c</sup> See Electronic Supplementary Material 6 for reference list.