# Identifying and evaluating patterns of prescription opioid use and associated risks in Ontario, Canada

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# Chapter 1:
# **Background**

## Prescription Opioids

Opioids are analgesics that have been used in clinical practice to treat acute and cancer-related pain since the beginning of the 20th century.[1,2] This class of medications includes natural (i.e. codeine and morphine), semi-synthetic (i.e. hydrocodone, hydromorphone, oxycodone) and synthetic drugs (i.e. fentanyl, methadone and others) that vary considerably in potency and are currently manufactured in a variety of formulations and strengths.[3] However, because of concerns around the potential risks of addiction when used over long periods of time, for most of the 20th century there was limited long-term use of these products.[1,4]

This changed in the 1980s following the release of two publications. The first, published as a letter in the New England Journal of Medicine in 1980 by Porter and Jick reported that among nearly 12,000 hospitalized patients treated with a narcotic, there were only 4 cases of addiction, all of which occurred among people with a history of addiction.[5] Despite the authors providing no methodological details for these reported findings, and the fact that the patients were treated with small doses of opioids in a controlled hospital setting for a short duration of time, this letter was widely used to support an assertion that less than 1% of opioid users develop an addiction.[6] Following this, in 1986 a case series by Portenoy and Foley was published describing 38 patients who had been treated with opioids for at least 6 months.[4] The objective of this study was to report on the course, safety and efficacy of chronic opioid therapy, with key measures including duration of use, dose prescribed, and adverse events. Due to a low number of measured serious adverse events, the authors concluded that opioid therapy initiated for the treatment of chronic non-cancer pain (CNCP) was safe and effective for long periods of time.[4] These conclusions were made despite the study's small size and restricted population (only 3 individuals had any psychiatric history). Furthermore, in 1986 the World Health Organization also released a report that introduced the WHO three-step ladder for cancer pain relief.[7] This ladder recommended that analgesics should be used incrementally, and that strong opioids like oral morphine should only be used to treat severe cancer pain. Despite being specific to cancer pain, this analgesic ladder was increasingly used by clinicians when treating chronic pain more generally.[8,9] This, in combination with the studies by Portenoy et al. (1986) and Porter et al. (1980), is broadly credited with justifying the notion that addiction to opioids was rare, thus driving the massive market expansion for opioids in North America in the 1990s.[6,8,9] In Canada, this was evidenced by a three-fold rise in the volume of opioid dispensing from 27.9mg morphine or equivalent (MME) per capita to 86.7 MME per capita between 1985 and 1996.[10]

In 1996, the opioid market shifted again when Health Canada approved a new, long-acting formulation of oxycodone – OxyContin®. This drug's manufacturer, Purdue Pharma, immediately implemented an intense marketing campaign for their new product in Canada and the United States, promoting broad use of opioids generally, and long-acting formulations for the treatment of CNCP, specifically.[11] A key component of this campaign was the company's claim that the risk of addiction to OxyContin® was small, that it provided patients with less of a 'high', and that there was no upper dose limit beyond that which was imposed by adverse events like respiratory depression.[11-13] Over the next decade, the introduction of OxyContin® drove a dramatic 1510% rise in oxycodone dispensing in Canada, from 8.5 MME per capita in 1996 to 136.5 MME per capita in 2005.[10] This contributed to a more general increase in opioid prescribing that was observed over this period, with the overall volume of opioids prescribed rising 450% from 86.7 MME per capita to 476 MME per capita over this same time period.[10] It quickly became apparent that OxyContin® tablets could easily be chewed, crushed or dissolved to circumvent its modified release formulation and produce a potent 'high'.[11,14] This in turn led to the emergence of an epidemic of prescription opioid misuse (intentional or unintentional drug use in a manner not consistent with medical indications or prescribed dosing), addiction (compulsive drug use characterized by difficulty in ceasing use despite harm) and diversion (redirection of prescription drugs to illicit market) across North America that continues to the present day.[15-18] In the United States in 2007, Purdue Pharma LLP pleaded guilty to a felony count of the misbranding of OxyContin® with the intent to defraud and mislead, and paid more than US $600 million in fines and restitution.[12,19] By 2014, almost 1000 MME of opioids was dispensed per capita in Canada, representing a nearly 50-fold increase from 1980.[10]

Despite the emergence of opioids to treat CNCP over the three decades since Portenoy and Foley's case series, there remains considerable debate as to the safety and efficacy of this practice. In particular, the evidence to support long-term use of opioid analgesics for chronic pain is limited, with a recent systematic review of randomized controlled trials concluding that there is a paucity of high quality evidence related to both efficacy and safety of opioids when used for longer than 12 weeks.[20] Furthermore, a systematic review of 38 prospective and retrospective studies in patients with CNCP found that rates of misuse and addiction to opioids were high, ranging from 21% to 29%, and 8% to 12%, respectively.[21]

## Effects of Opioid Use

Opioid analgesics alter the perception of pain by binding to mu-opioid, kappa-opioid and sigma receptors in the central nervous system (CNS).[22] However, in addition to their pain relieving properties, the opioid agonist activity can also lead to feelings of euphoria and sedation as well as decreased respiratory rate, nausea, vomiting, and attention impairment.[2,22] Furthermore, physical dependence can prevent people from discontinuing these drugs as they experience withdrawal symptoms (e.g. agitation, muscle aches, dysphoria and other symptoms).[2,23]

Concomitant use of opioids with other CNS depressants including sedatives, benzodiazepines and alcohol can enhance their sedating properties, leading to concerns regarding the risk of accidental overdose among individuals using multiple substances.[24-26] Indeed, a recently published case-cohort study among 2400 United States veterans who died of a drug overdose while using opioid analgesics found a nearly four-fold increased risk of drug overdose deaths among those concomitantly treated with benzodiazepines.[27] Similarly, a 2010 study found that approximately 1 in 5 emergency department (ED) visits related to opioid analgesics also involved alcohol.[28] As a result, most product monographs and clinical guidelines strongly recommend against concomitant use of opioids and other CNS depressants, and if necessary, suggest that dose adjustments are made to avoid risks of accidental overdose.[13,22,29,30]

## Opioid Use in North America

As of 2014, the United States and Canada had the highest volume of opioid prescribing per capita in the world, and drug overdose deaths were estimated to exceed those from motor vehicle accidents.[31,32] In the United States, the rate of opioid prescribing rose by more than 300% between 1999 and 2008[33], and in 2014, there were 28,647 drug overdose deaths involving opioids, representing almost two-thirds of all drug overdose deaths in the country.[34] Furthermore, for every death related to opioids, there are an estimated 32 emergency department visits related to opioid misuse, 130 people who are opioid dependent, and 825 non-medical opioid users, highlighting the broad societal impact of opioid misuse and related harm.[33] The economic burden of this has been estimated to be over $20 billion each year in the United States from both direct medical costs related to opioid poisoning treatment, as well as absenteeism and loss of future earnings from early mortality.[35]

In Canada, national data regarding opioid prescribing and related adverse events are sparse. National prescription volume data suggest that the volume of opioid prescribing (using defined daily doses: DDD) increased by 13% between 2005 to 2010 in Canada, and that dispensing of high dose formulations increased by 23% between 2006 and 2011.[36,37] Furthermore, these trends varied considerably across the country, with Quebec generally displaying the lowest rates of opioid prescribing, and Alberta and Ontario having the highest opioid prescribing rates.[36,37] More specific data relating to opioid prescribing and harms are available in Ontario, the most populous province in Canada, with a population of nearly 14 million in 2016 (approximately 39% of the total Canadian population[38]). A 2009 study by Dhalla et al. found that opioid prescription rates in Ontario increased 29% between 1991 and 2007, and that these increases were largely driven by an 850% rise in the rate of oxycodone prescribing following the introduction of OxyContin® to the provincial drug formulary in 2000.[39] This was mirrored by a 41% increase in the rate of opioid-related deaths between 1999 (prior to OxyContin's addition to the formulary) and 2004, half of which were accidental (52.4%). In another large population-based study among new users of opioids through the public drug program in Ontario, 11% continued therapy for 3 or more months, and approximately 1 in 550 of these chronic opioid users died of an opioid overdose over a median of 2.6 years.[40]

Finally, the implications of high opioid prescribing and resulting addiction in North America are far-reaching, including rising rates of neonatal abstinence syndrome (NAS) and increased illicit opioid use. NAS is characterized by tremors, increased irritability, poor feeding, vomiting and diarrhea in babies born to mothers who used opioids near the time of delivery[41], and between 2009 and 2012, rates in the United States rose from 3.4 to 5.8 per 1,000 hospital births.[42] Similarly, in Ontario, there was a 15-fold increase in the rate of NAS from 0.3 to 4.3 per 1,000 live births between 1992 and 2011 with the majority of this increase occurring after 2003.[43] Furthermore, there is concern that the emergence of opioid addiction over the past two decades is leading to increased use of illicit opioids like heroin, particularly as policies and regulations for prescription opioids are tightened. This is highlighted by a three-fold increase in the rate of heroin overdose deaths between 2010 and 2014 in the United States.[34] Although no similar data are available in Canada, it is expected that similar trends related to heroin have developed over the past several years.[44]

## Prescribing Guidelines For Chronic Non-Cancer Pain and Dose Thresholds

Despite the expanded use of opioids to treat CNCP in North America in the 1990s, little guidance was available for prescribers regarding the safe and appropriate prescribing of these medications for this indication. This was compounded by limited information in the product monographs for long-acting opioids like OxyContin® regarding appropriate dose limits.[13] In 2007, following reports highlighting particularly high rates of opioid prescribing and fatal overdoses in Washington State, the Washington State Agency Medical Directors' Group published a guideline on opioid dosing for CNCP that for the first time suggested a dose threshold for physicians.[45,46] The recommendation in this guideline was that the daily dose of opioid prescribed for CNCP should not exceed 120 MME daily and that this threshold should be surpassed only rarely, and after pain management consultation.[46] Due to limited evidence of the relationship between opioid dose and adverse events at the time, this guideline was largely informed by expert advice from state agencies and a physician panel. An evaluation of the impact of this guideline on prescribed opioid doses in Washington State found that, while the median daily dose dispensed per patient remained unchanged at 37.5 MME between 2006 and 2010, the proportion of individuals exceeding 60, 90 and 120 MME lowered over time.[45]

In 2010, the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain was released, and was based on a synthesis of the best available evidence at the time in conjunction with expert opinion where evidence was lacking.[30] This guideline represented the first time an opioid upper dose threshold was described in Canada, with a recommendation that CNCP could be managed in most patients at doses at or below 200 MME.[30] In the following years, a number of other jurisdictions released guidelines for opioids in CNCP that typically ranged between 100 MME and 200 MME.[47]

Most recently, in 2016, the United States Centers for Disease Control and Prevention (CDC) released national guidelines for prescribing opioids in chronic pain based on a systematic review of existing evidence, a contextual review of clinician and patient values and preferences, and expert opinion.[29] These new guidelines differed considerably from the 2007 Washington State guidelines in two ways. First, they specifically recommend against pharmacologic therapy as a first line option in managing chronic pain, and suggest that when opioids are used, they are combined with non-pharmacologic therapy, and non-opioid pharmacologic therapy.[29] Second, they recommend that a reassessment of the risks and benefits of opioid therapy be

conducted when considering daily doses exceeding 50 MME, and that clinicians generally avoid increasing dose beyond 90 MME.[29] Despite some controversy surrounding these guidelines,[48,49] they have been endorsed by physician groups and policy-makers both in the United States[50,51] and in some parts of Canada.[52,53]

## Key Shifts in Opioid Policy and Drug Availability

Over the past two decades, several policies and strategies have been developed in an attempt to curb the rising trends of opioid prescribing and overdose in Canada (Table 1.1). The first such strategy was introduced in November 2011 when Ontario's Narcotics Safety and Awareness Act (NSAA) came into force. The core objective of this act was to provide the provincial government with the ability to capture additional information regarding prescribing of controlled substances across Ontario to help identify and reduce misuse and diversion of these drugs and promote more appropriate prescribing and dispensing practices.[54] This legislation required prescribers to record specific information when prescribing these drugs (including prescriber and patient identifiers) and allowed the government to collect, use and disclose information related to prescribing and dispensing of monitored drugs in a Narcotics Monitoring System (NMS).[55] Historically, Ontario only collected this information for prescriptions reimbursed by the provincial drug program, and thus this represented the first time that prescription information for *all* opioids and other controlled substances was captured in Ontario. Although the NSAA legislation came into force in 2011, it wasn't until April 2012 that the NMS was implemented in pharmacies across Ontario. In October 2016, almost 5 years after the enactment of the NSAA, Ontario announced a new Opioid Strategy that extended beyond simply monitoring prescribing practices to include a number of additional initiatives including:

- Delisting high strength opioid formulations from the provincial drug program (as of January 2017);
- Expanding free access to naloxone – a medication used to block or reverse the effects of opioids, particularly among people who have overdosed - across the province;
- Increasing access to buprenorphine/naloxone for the treatment of opioid addiction;
- Implementing a fentanyl patch-for-patch program province-wide;
- Expanding and enhancing chronic pain clinics; and
- Developing evidence-based standards for opioid prescribing and addiction treatment.[56]

**Table 1.1**: Key policy changes related to prescription opioids impacting Canada over the past decade

| Guideline/Policy Change | Date |
|---|---|
| Washington State Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain | March 2007 |
| Canadian Guidelines for Opioids in Chronic Non-Cancer Pain released | April 30, 2010 |
| Tamper deterrent long-acting oxycodone introduced in the United States | August 2010 |
| Narcotics Safety and Awareness Act enacted in Ontario | November 1, 2011 |
| Narcotics Monitoring System introduced in Ontario | April 16, 2012 |
| Tamper deterrent long-acting oxycodone receives notice of compliance by Health Canada | August 22, 2011 |
| Tamper deterrent long-acting oxycodone introduced in Canada | February 29, 2012 |
| Generic long-acting oxycodone introduced in Canada | November 26, 2012 |
| United States CDC Guideline for Prescribing Opioids for Chronic Pain released | March 16, 2016 |
| Ontario Opioid Strategy announced | October 12, 2016 |

Finally, in November 2016, the Canadian federal government organized an opioid conference and summit which led to the release of a Joint Statement of Action to Address the Opioid Crisis.[57] This statement included commitments from Health Canada, provincial governments and key national and provincial stakeholders and included the implementation of Health Canada's Opioid Action Plan. This plan encompasses a number of initiatives such as improved patient education, restricted access to certain opioids, improved access to opioid addiction therapy and opioid–alternatives for pain management, and expanded evidence development to drive policy change.[57,58]

In addition to these policy initiatives, changes to drug formulations, patents and regulatory approvals for long-acting oxycodone have led to considerable shifts in the opioid prescribing landscape in Canada. The first such change occurred when the United States Food and Drug Administration (FDA) approved a tamper-deterrent form of long-acting oxycodone (Oxycontin-OP®) in April 2010. This drug was reformulated to make it more difficult to cut, break, chew, crush or dissolve and was thus described by the manufacturer as being more difficult to manipulate for the intention of misuse or abuse.[59] In August 2010, production of the original OxyContin® formulation ceased in the United States, and all pharmacies were supplied with the

new, tamper deterrent form of long-acting oxycodone. Given the widespread use of OxyContin® in the United States, and the high degree of misuse and diversion of this product, this led to concerns that United States citizens may cross the border into Canada where the original OxyContin® was still being manufactured. However, at the end of February 2012, OxyContin® was replaced with a tamper-deterrent form (OxyNeo®) in Canada[60], leading to a period when the only forms of long-acting oxycodone available in both countries had tamper-deterrent properties.

This changed when the patent for OxyContin® expired in Canada and the United States in November 2012 and April 2013, respectively. This created an opportunity for generic forms of long-acting oxycodone – with no tamper deterrent properties – to be once again manufactured. National regulatory agencies in the United States and Canada made different decisions regarding the approval for these generic forms. In the United States, the FDA announced that it would not accept or approve any forms of generic OxyContin® because its benefits no longer outweighed its risks.[61] In contrast, Health Canada authorized marketing of generic non-tamper-deterrent versions of long-acting oxycodone due to their bioequivalence to OxyContin® which they considered to be safe and effective after a review of the evidence.[62] Although most public drug programs across the country chose not to list generic long-acting oxycodone on their formularies[63,64], these products remain available in Canada for those individuals willing to pay out-of-pocket. This has led to alerts and requests from United States regulators for Canada to reconsider their approval of these drugs due to ongoing concern of drug trafficking across international borders.[65]

## Gaps in Knowledge

As the rate of opioid prescribing in North America has become an increasing concern over the past decade, policy-makers and clinicians have had little evidence to inform their decision-making regarding the safe use of these products. Despite the availability of some descriptive data from the United States, upon initiation of this thesis, there were considerable gaps in knowledge related to the burden of early loss of life due to opioid overdose, the relationship between escalating dose and adverse events, and the risks associated with concomitant use of opioids and other depressants of the central nervous system. Furthermore, as policies have been implemented, guidelines released, and new products approved in Canada, there has been an important need for ongoing evaluation of the impact and potential unintended consequences of

these changes to the opioid prescribing environment. The core objective of this thesis was to generate a body of research to address these gaps.

## Aims and Outline of Thesis

Opioid prescribing and related adverse events has been described as a public health emergency in Canada as the rate of opioid use continues to rise, and fatal overdoses claim the lives of thousands of Canadians each year. The core objective of this thesis is to describe patterns of opioid use across Ontario, to highlight clinically meaningful risks of opioid-related adverse events, and to evaluate the impact and potential unintended consequences of policy changes that have been implemented in Canada. The thesis is subdivided into 5 parts. Part I (Chapters 1 and 2) provides a general introduction to this issue, as well as an outline of the key objectives of studies included in the thesis and some overarching methodological details. In Part II (Chapters 3 and 4), we report the findings of descriptive studies designed to characterize patterns in opioid-related deaths, including those involving both opioids and alcohol. Part III (Chapters 5, 6, and 7) investigates the relationship between opioid use and adverse events, including fatal overdose and injury in a motor vehicle accident. Part IV (Chapters 8, 9, 10, and 11) explores the impact of changes to opioid availability, tamper deterrent formulations and provincial legislation on inappropriate opioid prescribing and non-fatal overdoses. Finally, in Part V (Chapter 12), the main findings, overarching methodological considerations, and future directions are summarized.

## Part II

In **Chapter 3**, trends in fatal opioid overdoses are explored between 1991 and 2010, with a specific focus on the public health burden of early loss of life due to opioid overdoses. This is examined through determination of the proportion of all deaths that are attributable to opioids overall in Ontario, and stratified by age group. Finally, the years of potential life lost due to opioids is estimated and contrasted against other common causes of death in Ontario.

In **Chapter 4**, the contribution of concomitant use of alcohol with opioids on fatal opioid overdoses is examined. Specifically, trends in the prevalence of alcohol-involved opioid overdose deaths are reported in Ontario, overall and stratified by manner of death (accidental, suicide and undetermined). Finally, characteristics of individuals who died from an opioid overdose with or without alcohol involvement are compared.

## Part III

**Chapter 5** reports the findings of a nested case-control study investigating the relationship between prescribed opioid dose and the risk of fatal overdose. This study explores the dose threshold outlined in the 2010 Canadian clinical guidelines (200 MME) as well as a number of lower dose categories compared to individuals prescribed less than 20 MME and provides evidence regarding risks of opioid overdose death as dose escalates.

In **Chapter 6**, the association between opioid dose and risk of injury in a motor vehicle accident (MVA) is studied to determine the extent to which simulation studies suggesting that opioid use is associated with decreased concentration and reaction time are translated to real world driving behaviour and risk of MVA. This association is explored among all individuals injured in motor vehicle accidents (including drivers, passengers and pedestrians) as well as in the subgroup of drivers, who are most likely to have opioids influence risk of an accident.

**Chapter 7** explores the potential drug-drug interaction between opioids and gabapentin, two central nervous system depressants often co-prescribed for pain. This study investigates whether, among individuals prescribed opioids, concomitant use of gabapentin increases the risk of an opioid-related death as a result of increased respiratory depression from the use of these two agents.

## Part IV

**Chapters 8 and 9** explore the impact of the introduction of new formulations of long-acting oxycodone on potential drug seeking behaviours across the United States-Canada border. Specifically, **Chapter 8** investigates whether there was any increase in dispensing of OxyContin® in Ontario regions close to the United States border after a tamper deterrent form of long-acting oxycodone replaced OxyContin® in the United States in 2010. **Chapter 9** then investigates whether any similar patterns were observed near any regions close to the United States border across Canada after the approval of generic forms of long-acting oxycodone in November 2012.

In **Chapter 10**, a study outlining trends in the rate of opioid use, the prevalence of individuals exceeding the upper dose threshold recommended in the 2010 Canadian clinical guidelines, and the rate of opioid-related hospital visits in Ontario is reported. We then measure the impact of the publication of the Canadian clinical guidelines and the enactment of NSAA on these patterns.

In **Chapter 11**, the impact of Ontario Narcotics Monitoring System on potentially inappropriate prescribing of monitored drugs is examined using a time series analysis. Potentially inappropriate prescriptions are defined as early refills for a drug that originate from a different prescriber and pharmacy. In this study, the prevalence of inappropriate prescribing of opioids, benzodiazepines and stimulants is investigated.

## Part V

**Chapter 12** summarizes the main findings of the research conducted, discusses overarching methodological considerations, and recommends future directions for research in this area.

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