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

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Chapter 12:
Discussion

Opioid prescribing and related adverse events are one of the key public health issues facing policy-makers in both the United States and Canada, leading to the loss of tens of thousands of lives annually. The core objective of this thesis was to inform and evaluate related drug-policy decision-making in Canada. This was accomplished by first describing patterns and public health impact of fatal opioid overdoses in Ontario by analyzing records for opioid-related deaths investigated by the provincial coroner's office. These studies described the growing rate of fatal opioid overdoses in Ontario, and the fact that these deaths are usually accidental in nature, are clustered among a younger demographic, and involve both opioids and other CNS depressants (including alcohol and other drugs). Furthermore, the public health burden of this early loss of life is considerable, with nearly 22,000 years of potential life lost in 2010 due to opioid overdoses. Next, we used opioid prescribing data to look at the relationship between patterns of opioid use and adverse events. These studies demonstrated that increasing opioid doses are associated with both fatal overdose deaths and risk of being injured in a motor vehicle accident when driving. Furthermore, in an analysis exploring the risks associated with concomitant use of CNS depressants, we found a significantly increased risk of opioid-related death among patients concomitantly using opioids and gabapentin. Finally, we explored the impact of new opioid formulations and legislation on patterns of opioid prescribing, dispensing and adverse events. In these studies, we found indications of elevated OxyContin® dispensing at Ontario pharmacies near the Detroit-Windsor tunnel following the introduction of tamper-deterrent long-acting oxycodone in the United States, but no similar shifts in dispensing patterns upon the introduction of generic long-acting oxycodone in Canada several years later. Furthermore, we found that legislation introduced in Ontario had a significant impact on inappropriate prescribing of opioids, but no impact on rates of hospital visits for opioid overdoses.

Summary

Part II of this thesis (**Chapters 3 and 4**) reports the findings of descriptive studies designed to characterize patterns in fatal opioid overdoses in Ontario.

In **Chapter 3**, we presented a descriptive study on opioid-related deaths in Ontario between 1991 and 2010, and estimated the burden of this early loss of life using years of life lost (YLL).[1] We found that the rate of opioid-related deaths increased by 242% over the 20 year study period, almost two-thirds (64.4%) of decedents were men, and the average age at time of death was 42 years. The estimated YLL due to premature death involving opioids increased three-fold between 1992 (7,006 years) and 2010 (21,927 years). The proportion of all deaths attributable to opioids also increased significantly within each age group studied. By 2010, 1 in 170 deaths in Ontario was attributable to opioids, and in the subgroup of young adults (aged 25 to 34 years), 1 in 8 deaths was attributable to opioids. This study was the first to characterize the burden of opioid related deaths using coronial records, and helped highlight the impact of accidental early loss of life due to opioid overdoses in Ontario.

In **Chapter 4** we expanded on the work presented in **Chapter 3** by examining temporal trends and clinical characteristics of opioid-related deaths with and without concomitant alcohol use. Among the 6,702 opioid-related deaths from 1993 to 2013, we found that the proportion with alcohol involvement became lower over time, falling from 37.8% of all opioid-related deaths in 1993 to 21.9% in 2013. This was largely a consequence of increased rates of accidental opioid-related deaths not involving alcohol, which rose 615% from 3.9 deaths per million in 1993 to 28.1 deaths per million in 2013. Accidental deaths involving alcohol also increased over the study period, but to a much smaller degree, rising 174% and reaching 8.2 deaths per million in 2013. Among those opioid-related deaths involving alcohol, the median blood alcohol concentration (BAC) in post-mortem toxicology was 0.14g/dL, a level lower than those generally found to cause death by acute alcohol intoxication, but high enough to lead to clinically relevant physiological and behavioural effects. Furthermore, other drugs were regularly identified in post-mortem toxicology, including benzodiazepines and tricyclic antidepressants. The findings of this study highlight the avoidable nature of a large proportion of opioid-related deaths in Ontario, and the high degree of concomitant use of alcohol and other CNS depressants at time of death.

Part III (**Chapters 5, 6, and 7**) investigates the relationship between opioid use and adverse events, including fatal overdose and road trauma.

In **Chapter 5**, we report the findings of a nested case-control study among a cohort of Ontario residents aged 15 to 64 years who were dispensed a prescription opioid reimbursed through the provincial public drug program. After extensive multivariate adjustment, we found that daily doses exceeding the threshold described in the 2010 Canadian clinical guidelines (200 MME]) were associated with a nearly threefold increase in the odds of opioid-related mortality compared to low daily doses (<20 MME; aOR 2.88; 95% CI 1.79 to 4.63).[2] Importantly, even moderately high daily doses (50-199 MME) were associated with a doubling of the odds of opioid-related death. These findings carry considerable implications as they show a clear association between opioid doses advised by clinical practice guidelines and the risk of fatal overdose.

In **Chapter 6**, we used a design similar to the one employed in **Chapter 5** to explore the relationship between opioid dose and motor vehicle accidents (MVAs). In this study, we used data from emergency departments in Ontario to identify individuals injured in an MVA who were also being dispensed opioids.[3] Among 549,878 eligible adult patients, we identified 5,300 people injured in an MVA. In our primary analysis among all MVA injuries (regardless of whether the person injured was driving the vehicle), we found no association between prescribed opioid dose and injury. However, in a secondary analysis among drivers, we found that doses exceeding 20 MME were associated with a 20-42% increased odds of road trauma compared to those dispensed less than 20 MME daily. Although we did not observe a clear dose-response relationship, the findings are consistent with driver simulation studies, and suggest that moderate and high doses of opioids can impair drivers and lead to important risks of injury from motor vehicle accidents.

Finally, in **Chapter 7**, we again employed a nested case-control design to explore risks of opioid-related deaths. In this study among adults dispensed opioids through the provincial drug program, we explored whether concomitant use of gabapentin – an anticonvulsant commonly used with opioids as an adjunct for the treatment of chronic pain – increased the risk of opioid-related death. After multivariable adjustment (including adjustment for prescribed opioid dose), we found that co-prescription of opioids and gabapentin was associated with a 49% increased odds of opioid-related death compared to use of opioids alone (aOR 1.49; 95% CI 1.18 to 1.88) and that very high dose gabapentin was associated with a nearly two-fold increase of these odds. These findings likely reflect both a phar-

macodynamic and pharmacokinetic interaction between opioids and gabapentin through enhanced respiratory depression and increased gabapentin bioavailability. Importantly, in a sensitivity analysis testing the specificity of our findings, we found no such association with co-prescribed NSAIDs (aOR 1.14; 95% CI 0.98 to 1.32). This study highlights an important drug-drug interaction with considerable clinical consequences, because almost half of gabapentin recipients in Ontario received at least one concomitant opioid prescription and nearly 1 in 10 opioid users had recently received a prescription for gabapentin.

Part IV (**Chapters 8** through **11**) explores the impact of changes to opioid availability, the introduction of tamper-deterrent formulations, and provincial legislation on inappropriate opioid prescribing and adverse events. In particular, **Chapters 8** and **9** use population-based data across Canada to explore how differing availability of long-acting oxycodone formulations across the United States-Canada border led to changes in dispensing patterns that may be indicative of cross-border drug trafficking.[4,5] In **Chapters 10** and **11**, we then explore the impact of the Canadian opioid prescribing guidelines and Ontario's Narcotics Safety and Awareness Act (NSAA) on trends in opioid prescribing and overdose.[6]

In August 2010, a tamper-deterrent form of long-acting oxycodone was introduced in the United States that was not introduced in Canada until February 2012. In **Chapter 8**, we investigated the impact of this differential access to OxyContin® on dispensing patterns from pharmacies close to the 6 highest volume United States-Ontario border crossings.[4] Over 3.5 million OxyContin® tablets were dispensed in these regions over the 23 month study period, equivalent to more than 5,200 tablets each day. Among 5 of the border crossings investigated (captured in 4 dispensing regions), dispensing of OxyContin® remained stable over our study period. However, near the Detroit-Windsor Tunnel, the rate of OxyContin® dispensing increased immediately following the introduction of tamper-deterrent forms in August 2010 in the United States, and continued to rise until warnings of potential drug-seeking behaviour were sent to prescribers and pharmacies in the region in March and April of 2011. In total, we estimated that the elevated dispensing rate led to approximately 250,000 additional OxyContin® tablets being dispensed near the Detroit-Windsor Tunnel between August 2010 and November 2011.

In November 2012, Health Canada authorized the marketing of generic non-tamper-deterrent long-acting oxycodone. In contrast, the United States Food and Drug Administration did not approve these generic formulations. In **Chapter 9**, we explore whether the differential availability of non-tamper-deterrent forms of long-acting

oxycodone led to increased sales in Canada near the United States border.[5] In this study, we investigated dispensing patterns for long-acting oxycodone close to 113 border crossings in 50 dispensing regions across Canada. In contrast with our findings in **Chapter 8**, we found no substantial fluctuations in dispensing patterns for long-acting oxycodone in any of the regions studied. Small increases were observed in four Ontario border crossings (Feree Pelee, Rainy River, Buffalo-Queenston, and Detroit Windsor Tunnel), however the increases did not occur until long after the introduction of generic long-acting oxycodone and were associated with only a small rise in the number of tablets dispensed. No increases were observed in any other border crossings studied. In sensitivity analyses, we found no indication of increased long-acting oxycodone dispensing in larger cities close to the United States-Canada border, or among a subgroup of regions bordering High Intensity Drug Trafficking Areas in the United States.

Chapter 10 reports findings from an interventional time-series analysis of rates of opioid prescribing and overdose-related hospital visits in Ontario. Between 2003 and 2014, the rate of opioid prescribing in Ontario declined by 15.2%, and was significantly impacted by the publication of the Canadian clinical practice guidelines ($p=0.03$). The enactment of NSAA led to no further observed changes in these trends ($p=0.43$). In contrast, rates of opioid-related hospital visits increased 55% between 2003 and 2013, and were not impacted by the guidelines ($p=0.68$) or NSAA ($p=0.59$). Importantly, the prevalence of opioid prescribing at daily doses exceeding thresholds from clinical guidelines (200 MME) increased from 4.2% to a high of 10.0% at the end of 2011, before falling slightly to 8.7% in 2014. High dose opioid prescribing was most prevalent among long-acting opioid users, 41% of whom received more than 200 MME and almost 20% of whom received more than 400 MME in 2014. This study demonstrates that – although there was a small decline in the rate of opioid prescribing following the publication of Canadian guidelines – use of opioids at high doses remains common practice in Ontario. This may explain the continued pervasiveness of hospital visits for opioid toxicity over this time. These findings suggest that improvements in policies and programs related to opioid prescribing – particularly at high doses – are needed.

Finally, in **Chapter 11**, we investigate the impact of Ontario's Narcotics Safety and Awareness Act (NSAA) and its prescription monitoring program (Narcotics Monitoring System; NMS) in 2011 on inappropriate prescribing of monitored drugs among public drug beneficiaries in Ontario.[6] Drug classes explored in this study included opioids, benzodiazepines and stimulants. Inappropriate prescribing was

defined in our primary analysis as an early refill of a drug in the same class but issued by a different physician and dispensed at a different pharmacy than the original prescription. Overall, we found that 1.6% of opioid prescriptions, 0.4% of benzodiazepine prescriptions, and 0.7% of stimulant prescription met these criteria over our entire study period. Both enactment of the NSAA and introduction of the NMS resulted in significant reductions in the prevalence of prescriptions for opioids and other controlled substances that are highly likely to represent misuse. Although 1% of dispensed opioid prescriptions continued to meet this definition of potentially inappropriate use at the end of our study, the findings demonstrate that legislation and improved monitoring by healthcare professionals can have a measurable impact on potentially harmful prescribing behaviours.

General Discussion

Four core themes of this thesis that merit additional discussion include the role of opioid dose in adverse events, the public health burden of opioid-related deaths, the contribution of concomitant use of other CNS depressants to this issue, and the impact of newly introduced drug policies.

OPIOID DOSE

Appropriate dosing of opioids and the establishment of dose thresholds has been an area of considerable debate and interest over the past several decades as clinicians have looked for direction on effective and safe prescribing practice. Despite the inclusion of upper dose thresholds in opioid prescribing guidelines published between 2007 and 2010, there was little evidence to support these recommendations outside of advice from expert panels.[7,8] The studies reported in **Chapters 5 and 6** of this thesis were among the first to characterize the relationship between opioid dose and adverse events. Our finding of elevated risk of opioid-related death among individuals using moderately high opioid doses is consistent with other literature in this area that has been published since 2010. For example, Dunn and colleagues published a cohort study among chronic opioid users in 2010 that estimated the risk of fatal and non-fatal overdose.[9] Although this study was small (only 6 fatal opioid overdoses recorded), they found a significant association between escalating opioid doses and the risk of overdose. Specifically, compared to daily doses below 20 MME, doses between 50 and 99 MME were associated with a 3.7-fold increased risk of overdose, and doses of 100 MME or more were associated with a nearly 9-fold increased risk of overdose.[9] The following year, Bohnert and

colleagues reported findings from a case-cohort study investigating the relationship between opioid dose and opioid-related death using a large Veterans Affairs cohort.[10] In this study, doses above 50 MME were associated with increased risks of fatal opioid overdoses among all patient populations studied, including those with chronic non-cancer pain, cancer pain, acute pain and substance use disorders.[10] Our study, published at the same time as the Bohnert study, also reported a significant association between opioid doses above 50 MME and fatal overdose deaths, although the strength of association was not as pronounced.[2] Interestingly, despite clinical guidelines at the time having recommended upper dose thresholds between 100 and 200 MME, all three of these studies demonstrated considerably increased risks of fatal and non-fatal overdoses when opioids were prescribed above 50 MME.

Our findings related to opioid dose and risks of road trauma strengthen the body of research regarding opioid-related adverse events. Prior to this publication, studies investigating the impact of opioids on driving ability were restricted to small randomized controlled trials (RCTs) of driving simulations[11,12] and observational studies using data from registries.[13-18] The results of these studies were inconsistent, like reflecting differences in comparator groups and study populations, as well as the dose, type and duration of opioid used. In order to address some of these issues, we used a population-based study design, and analyzed both dose of opioid prescribed as well as risks among new opioid users. Our finding of a 21-42% elevated risk of road trauma among those prescribed over 20 MME[3] aligns with estimates from a case-control study of unsafe driver actions among opioid users compared to non-users (aOR 1.72; 95% CI 1.45 to 2.03).[13] Furthermore, both our study and an RCT among opioid naïve individuals found no association between opioid initiation and risk of road trauma[3] or driving performance[11], suggesting that the driving risks associated with opioid use may be tied to dose, and not opioid initiation.

In totality, the studies reported in **Chapters 5 and 6** of this thesis highlight the degree to which opioid doses considered to be 'moderate' over the past decade are contributing to serious adverse events in Ontario. These findings are of considerable importance given the degree to which opioids are prescribed at high doses in Ontario. Indeed, 9% of publicly-funded opioid users in Ontario were prescribed daily doses exceeding 200 MME, representing almost 13,000 people at the end of 2014.[19] Furthermore, among individuals prescribed long-acting opioids, this prevalence was over 40% (12,351 of 30,228 long-acting opioid users). In 2016, the United States CDC published revised guidelines for opioid prescribing in CNCP that recommend

a reassessment of the risks and benefits of opioid therapy when considering daily doses exceeding 50 MME, and a general avoidance of daily doses beyond 90 MME.[20] Both studies reported in **Chapters 5 and 6** were cited in these guidelines as evidence to support these lower dose thresholds.

BURDEN OF OPIOID-RELATED DEATHS

In Ontario, the number of opioid-related deaths in 2013 (N=638) exceeded the number of fatal motor vehicle accidents in this province (N=518), highlighting the public health importance of this issue.[21,22] Furthermore, in contrast to declining rates of motor vehicle collision fatalities[21], trends in opioid-overdose deaths continue to rise. In the United States, opioid overdose rates nearly quadrupled between 1999 and 2011, rising from 14 to 54 deaths per million population.[23] In Ontario, we have observed similar trends. For example, from 1991 to 2010, there was a more than three-fold increase in the rate of opioid-related deaths (242%) in Ontario, rising from 12 to 42 deaths per million population.[1] While this rising trend is similar to that reported in the United States, the magnitude of the rates in Ontario is slightly lower. Similarly, in other jurisdictions outside of North America, the rates of opioid overdoses also appear to be on the rise.[24,25] For example, in England and Wales, the number of opioid-related deaths increased 38% from 1,439 to 1,989 between 2011 and 2015.[24] Similarly, in Sweden, there was a 59% increase in the number of opioid-related deaths from 2011 to 2014.[25] In England and Wales, the rate of opioid-related death remains slightly lower (34 deaths per million population in England and Wales) than rates in North America, while in Sweden, rates are similar (52 deaths per million population in Sweden).[1,23-25] However, in most European countries the increase in opioid prescribing has been much lower than in the United States and Canada, and in many of these countries there has been no increase in prescription opioid related deaths. A number of possible explanations are provided for these transatlantic differences, including differences in the regulation of prescription drugs, the availability of illicit drugs, pharmaceutical advertising, governmental licit and illicit drug policy, regulatory frameworks for pharmaceutical drugs, and the availability and accessibility of opioid substitution treatment.[26] Furthermore, the emergence of bootleg fentanyl analogues to the North American illicit drug market has driven increased opioid overdoses in some jurisdictions in recent years due to its potency and relative ease of accessibility.[27] This has led to calls for an expanded collaborative approach to the opioid crisis in North America, including both public health and law enforcement to address the burgeoning illicit opioid supply.[27,28]

The early loss of life from opioid overdose imposes a considerable burden on society, particularly given the young age at which many North Americans are dying of opioid-related causes.[1,23] In the United States, the economic burden of opioid-related poisonings has been estimated to exceed $20 billion annually, with the majority of these costs coming from loss of future earnings.[29] In Canada, while opioid-specific cost studies have not been completed, a 2002 study estimated that the economic impact of substance abuse was nearly $40 billion, and that of illegal drugs was $8.2 billion, annually.[30,31] Furthermore, the Global Burden of Disease (GBD) Study's 2010 report estimated that 3.6 million years of life were lost worldwide due to harmful use and dependence on opioids and cocaine.[32] In our study, in Ontario alone, almost 22,000 years of life were lost (YLL) due to opioid overdose deaths in 2010, a more than three-fold rise since 1992.[1] If we extrapolate these findings to Canada, we estimate that almost 60,000 YLL are attributable to opioid overdoses each year. In the United States, where rates of opioid-related deaths are similar, we estimate that more than half a million years of life are lost to opioid overdoses annually.

Finally, the societal burden of opioid overdose is not confined to fatal overdoses. Opioid-related hospital visits have risen 55.6% among public drug beneficiaries in Ontario between 2003 and 2013[19], and in 2014 there were 3,241 opioid-related emergency department (ED) visits and 1,620 inpatient hospital admissions for opioid toxicity in Ontario.[22] This amounts to approximately 5 opioid-related hospital visits for every overdose death that occurs in Ontario. In the United States, these estimates are even higher, with the CDC reporting 32 ED visits and 825 non-medical opioid users for every opioid overdose death that occurred in 2008.[33]

USE OF OPIOIDS WITH OTHER CNS DEPRESSANTS

The concomitant use of opioids with other depressants of the central nervous system (CNS) has been the focus of growing attention as it has become apparent that the majority of overdose deaths involve opioids in combination with other substances.[34,35] Two such substances are reported in this thesis: gabapentin and alcohol.

Gabapentin

Gabapentin is an anticonvulsant used to treat chronic pain that, although widely perceived as relatively safe, has led to warnings regarding potentially dangerous respiratory depression when used in combination with other drugs like opioids.[36-39]

Literature in this area suggests that the potential drug-drug interaction between opioids and gabapentin is both pharmacodynamic and pharmacokinetic in nature.[40] Specifically, given the CNS depressing properties of both drugs, they have the potential to induce more severe, and possibly dangerous or even fatal, respiratory depression when used together. Furthermore, given the degree to which gabapentin absorption is mediated by the L-type amino acid transporter 1 (LAT1) in the upper small intestine, the slowing of gastrointestinal transit of gabapentin when co-prescribed with opioids has been shown to increase gabapentin bioavailability.[40] The findings of our study reported in **Chapter 7** highlight the clinical importance of this drug-drug interaction. Specifically, we found that co-prescription with opioids and gabapentin was associated with a 49% increased risk of opioid-related death compared to individuals treated with opioids alone. Furthermore, very high dose gabapentin use was associated with a nearly two-fold increased risk of opioid-related death. Although product monographs for gabapentin issue warnings of increased side effects – including fatal cases of respiratory depression – there has been little evidence in the literature to demonstrate the extent of this interaction outside of case reports.[37,38] Given the high degree of concomitant use of these drugs (8% of opioid users have recently been prescribed gabapentin), these findings provide important information to clinicians who are treating patients for chronic pain and may be considering the use of these two drugs.

Alcohol

In the United States, it is estimated that 17 million people have an alcohol use disorder, and almost 90,000 people die from alcohol-related causes each year.[41] Furthermore, concurrent use of alcohol and opioids is high, particularly among chronic opioid users where rates are estimated to exceed 12% in the United States.[42] Due to the risks of potentially fatal respiratory depression, opioid prescribing guidelines recommend that physicians review the risks of mixing opioids and alcohol with their patients[7,8,20]. Our study reported in **Chapter 4** is unique because it used findings from post-mortem toxicology to assess the extent to which alcohol is contributing to opioid-related deaths in Ontario, and how this differs based on manner of death. Importantly, we found that although 1 in 5 opioid-related deaths in 2013 involved alcohol, the prevalence of alcohol involvement in these deaths has fallen considerably, from 37.8% in 1993 to 21.9% in 2013. While alcohol-involved opioid-related deaths were less likely to also involve other CNS depressants, the prevalence of the use of benzodiazepines (42.4%), tricyclic

antidepressants (13.4%) and antihistamines (13.4%) in these deaths was high. The fact that over two-thirds of these deaths were accidental in nature highlights the largely avoidable nature of opioid-related deaths in Ontario and the need for targeted messaging regarding risks involved with the use of alcohol and other CNS depressants among opioid users.

MEASURING IMPACT OF DRUG POLICY

Cross-border Trafficking

The potential for national drug policy decisions to have implications across international borders is a chief concern for government officials in both Canada and the United States given the expansiveness of the international border, and differences in opioid drug policy. This is underscored by differences in the timing of approvals for both tamper-deterrent and generic forms of long-acting oxycodone.[43-46] This thesis presents the findings of two studies designed to measure the extent to which differences in availability of long-acting oxycodone formulations led to dispensing behaviours indicative of cross-border trafficking of this drug. In the first study, we examined 6 border crossings between Ontario and the United States[4] and found no suggestion of increased OxyContin® dispensing once the tamper-deterrent form was introduced in the United States in 5 of these border crossings. However, near the Detroit-Windsor Tunnel, we found an immediate rise in dispensing of OxyContin® from the 14 pharmacies operating in this area. The dispensing of OxyContin® continued to rise until the College of Physicians and Surgeons of Ontario and the Ontario College of Pharmacists issued warnings to their constituents in early 2011 that Canadian OxyContin® may be sought for diversion to the United States. Over the course of this period of elevated dispensing, almost 250,000 excess OxyContin® tablets were dispensed near the Detroit-Windsor Tunnel. These findings are of particular interest because of the specificity of the finding – even the Ambassador Bridge, which also connects Detroit and Windsor, did not see elevated dispensing of OxyContin®. We hypothesized that the dispensing behaviour near the Detroit-Windsor Tunnel was likely due to one of a number of factors. First, Detroit is the epicenter of the Michigan High Intensity Drug Trafficking Area (HIDTA), and as such acts as the primary distribution centre for the region.[47] As a result, it is not unexpected that drug-seeking behaviour originates from this area. The differences between the Detroit-Windsor Tunnel and Ambassador Bridge are more difficult to explain, however the Tunnel does not generally carry commercial traffic, and connects directly to the downtown Detroit

core. Second, we are unable to examine dispensing by individual pharmacies, but it is possible that a small number of the 14 pharmacies operating near the Detroit-Windsor Tunnel were responsible for this elevated dispensing behaviour. Therefore, our findings may be reflective of individual drug trafficking behaviours and transportation patterns in the downtown Detroit area, rather than of broader national trafficking patterns.

This is reinforced by the findings of our second cross-border study reported in **Chapter 9** which explored whether there were any other similar dispensing patterns after generic forms of non-tamper deterrent long-acting oxycodone were introduced in Canada in December 2012. In this study, we obtained data for 50 dispensing regions near 113 border crossings across Canada.[5] Despite the broad geographic scope of this analysis, we found no dispensing patterns suggestive of drug-seeking behaviour in the year following the introduction of generic long-acting oxycodone. We hypothesized that these contrasting findings may reflect several factors, including the slow adoption of generic formulations for these drugs in most regions of Canada, broader appreciation in the medical community about the potential for cross-border drug-seeking behaviour and/or the potential for our methods to have missed this behaviour if drug traffickers focused on accessing these drugs from larger city centres. We considered this latter point because many of the Canadian cities bordering the United States are rural, with a small number of pharmacies operating in these regions. As a result, it is possible that individuals looking to move these drugs across the border would be more likely to operate in larger cities where the higher dispensing patterns may be less prone to detection. To investigate this further, we conducted a sensitivity analysis among the two largest cities close to the United States-Canada border in each province in Canada. In this analysis, we similarly found no indication of increased dispensing of generic long-acting oxycodone in the year following its introduction. Despite this finding, given our inability to identify stolen long-acting oxycodone, and the potential for broader availability of generic forms of long-acting oxycodone in the future, we recommend that physicians and pharmacists remain vigilant in assessing the potential for drug-seeking behaviour when prescribing and dispensing these generic products.

Overall, the findings of these two studies highlight the complexity of measuring the cross-border implications of drug policy decisions, and their potentially localized impact. Furthermore, they suggest an interesting, novel approach to monitoring indicators of drug trafficking across international borders.

Narcotics Safety and Awareness Act

Two of the studies reported in this thesis explored the impact of the Narcotics Safety and Awareness Act (NSAA) and the accompanying Narcotics Monitoring System (NMS) on prescribing behaviour and patient outcomes. This work suggests that, although the NSAA did not impact overall trends in rates of publicly-funded opioid prescribing in Ontario ($p=0.43$)[19], it did impact patterns of potentially inappropriate opioid prescribing, defined as an early refill for an opioid that originated from a different prescriber and pharmacy.[6] Specifically, the prevalence of potentially inappropriate opioid prescribing fell from 1.84% prior to enactment of the NSAA to 0.95% by May 2013.[6] However, despite this, there remained approximately 10,000 prescriptions dispensed in May 2013 that were suggestive of inappropriate use. Therefore, although Ontario's opioid strategy did lead to measurable decreases in concerning opioid prescribing behaviour, considerable issues remain. For example, there are two key limitations to the NMS that may have limited the impact of this policy change. First, while dispensing behaviour for an individual is linked in the system regardless of which pharmacy they attend, the NMS allows patients to use one of a number of different forms of identification when obtaining their opioid prescription. Unfortunately, the system is incapable of linking these pieces of identification internally. Therefore, someone can use a drivers' license at one pharmacy and a health card at another, and the system would treat them as two separate individuals. This is a key limitation, as it would allow people to avoid the warning systems built into the NMS. Second, the NMS is currently only accessible to pharmacists at the time of dispensing a drug. Therefore, prescribers are unable to access information regarding potential drug-seeking behaviour of patients they are treating. This is of particular concern for physicians working in emergency departments and walk-in clinics who may not have a detailed clinical profile of the patients who they are treating. Emergency departments in Ontario currently have access to data on prescription drugs that are reimbursed by the government to ODB eligible individuals. Therefore, expansion of this infrastructure to incorporate all drugs monitored by the NMS would be a considerable improvement. Furthermore, as primary care physicians move towards electronic medical records, incorporating access to the NMS into these systems may be an appropriate means of expanding access to primary care and walk-in clinics in the province.

Our findings in Ontario align with those reported elsewhere in Canada. In British Columbia, a similar definition of inappropriate dispensing was used to evaluate the impact of their PharmaNet system on inappropriate opioid prescribing.[48] This study

similarly found a reduction in the prevalence of this behaviour, falling from an average of 3.2% prior to PharmaNet's introduction to approximately 2% a year and a half later.[48] Despite the similar findings, in British Columbia the changes in inappropriate opioid dispensing appeared to occur more rapidly than what we observed in Ontario. It is possible that this is due to the stepwise implementation of the NSAA (November 2011) and the NMS (May 2012), leading to a more gradual shift in practice in Ontario. Prescription monitoring programs have been implemented across the United States with varying effectiveness. Although evaluations of their impact on inappropriate opioid use have not been conducted, programs that are most successful at reducing the volume of opioid dispensed are governed by departments of health, which aligns with the approach taken in Ontario.[49]

Methodological Considerations

THESIS STRENGTHS

There are several strengths to the studies reported in this thesis, the most important being the large, population-based nature of the analyses. Ontario is the most populous province in Canada, with a population of nearly 14 million residents in 2016.[50] The studies reported in Chapters **3, 4, 8** and **9** used administrative and clinical databases that are complete for the entire provincial population, and are therefore generalizable broadly across Ontario. Furthermore, the remaining chapters in this thesis were conducted among the entire population of nearly 4 million Ontarians eligible for publicly-funded medications.

Of particular importance is our ability to link death data from the Office of the Chief Coroner of Ontario (OCCO) to other administrative databases in these studies. Coronial records, including post-mortem toxicology, are considered to be the best method for determining opioid-related deaths, but have not been broadly available for research purposes in North America due to difficulties in accessing, abstracting, and linking this sensitive information. Through an ongoing relationship with the OCCO, we have obtained data related to fatal opioid overdoses occurring over the past 2 decades, which has allowed us to conduct a number of important clinical studies of risk factors for opioid-related death. To our knowledge, this is the largest database of opioid-related death data sourced from coronial records that is linked to other population-based health databases in North America.

Finally, the Institute for Clinical Evaluative Sciences (ICES) in Ontario houses a large repository of linked health administrative data for research purposes. Seven of the 9 studies reported in this thesis used these linked databases, allowing

us to access rich clinical information for individuals included in these analyses. Specifically, this includes diagnosis and procedure data for all emergency department visits and inpatient hospitalizations, cancer diagnoses, physician billing information, publicly-funded medication dispensing details and vital statistics for all Ontario residents over the past 25 years. Through linkage of this data, we are able to define and adjust for a large number of potential confounders in each of our studies.

THESIS LIMITATIONS

Despite the numerous strengths outlined above, there are several general limitations to the studies reported in this thesis that merit consideration.

Unmeasured Confounders

The studies reported in this thesis are observational in nature, and largely rely on administrative databases to define patient populations and ascertain their clinical characteristics. Therefore, although we are able to capture a large number of potential confounders in our analyses, there are some patient characteristics that we are not able to define. Examples of these include indication for opioid therapy, severity of pain, and personal or familial history of substance abuse. As a result, we have developed a number of methods for addressing this, including restricting our study cohorts to those with non-cancer pain (through exclusion of individuals with a history of cancer diagnoses or palliative care services) and matching on disease risk scores in nested-case-control studies.

Generalizability

In some of the studies reported in this thesis (**Chapters 5, 6, 7, 10, 11**), our analyses were restricted to individuals aged less than 65 years who were eligible for public drug coverage in Ontario in order to access medication dispensing history. In Ontario, eligibility for public drug coverage in this age group is limited to low income individuals, recipients of disability support or home care, and those with high drug costs compared to household income. Therefore, these findings may not be generalizable to other populations. This is likely of greatest importance in **Chapter 10**, which examines patterns of high dose opioid use and hospital visits for opioid toxicity. While it is possible that some of these patterns are similar in the broader population of opioid users in Ontario, it is likely that people eligible for public drug benefits may have higher rates of pain and history of substance use disorders, which could limit the generalizability of these trends.

Private and Cash Medication Payment

In the studies that restricted the patient population to those eligible for public drug coverage, we are unable to determine whether these same patients received additional opioids through private insurance or cash payment. This could have impacted our studies in two ways. First, our calculated average daily dose of opioid prescribed is only based on dispensing records for reimbursed medications. Therefore, if patients obtained additional opioids through other payment mechanisms, our dose calculations may underestimate the true dose dispensed. Furthermore, in **Chapter 11**, it is possible that some patients continued to receive potentially inappropriate opioid prescriptions, but that they were paying for these additional prescriptions with cash. Therefore, the results of this study must be interpreted as demonstrating a reduction in potentially inappropriate prescribing of *publicly-funded* opioids in Ontario following the introduction of the NSAA and NMS.

Illicit Opioid Involvement

We are unable to determine the extent to which opioid overdoses were due to prescribed opioids vs. illicit opioids. In particular, prescription opioids identified on post-mortem toxicology (i.e. oxycodone, morphine), could have originated from a prescription for that patient, or may have been obtained through diverted prescription medications. Furthermore, we are unable to accurately differentiate between prescribed and clandestinely-manufactured fentanyl. Finally, as new opioids are being manufactured and sold illegally in Canada, it is not always possible to undertake post-mortem testing for these agents. Therefore, we may not capture involvement of some emerging agents (e.g. carfentanil) in our analyses, although it is expected that their involvement would be rare during the time frame considered in this thesis.

Adverse Selection

Research published by Edlund et al. investigating mental health and substance use disorders among chronic opioid users suggests that these patient populations are more likely to receive high dose opioid therapy over a long duration.[51] Therefore, it is possible that 'adverse selection' – the tendency for patients with substance abuse disorders and mental health conditions to receive chronic opioid therapy – may have influenced the findings of some of our opioid dose analyses. We addressed this to the best of our ability through matching on a disease risk index in **Chapters 5 and 6**, and adjusting our multivariate models for any remaining

unbalanced confounders. However, it is possible that this selection could contribute to the observed relationship between opioid dose and risk of adverse events.

Aggregated IMS Brogan Geographic Prescription Monitor Data

We used aggregated data obtained from IMS Brogan to conduct the analyses of opioid dispensing patterns close to the United States-Canada border. One limitation of these data is that we are unable to determine whether medications were dispensed to residents of Canada or the United States. Therefore, while we hypothesize in **Chapter 8** that the spike in OxyContin® dispensing close to the Detroit-Windsor Tunnel reflected cross-border drug seeking behaviour, we cannot confirm that these tablets were actually dispensed to United States citizens.

Opioid Conversion Ratios

We used morphine equivalence ratios to convert the volume of opioids dispensed into milligrams of morphine equivalents (MME). Although there is some variation in published conversion ratios for some opioids, we restricted our dose analyses to drugs where these ratios are well defined.[8,52] These opioids (oral oxycodone, hydromorphone, morphine, codeine, meperidine and transdermal fentanyl) represent the vast majority of opioids dispensed through the ODB in Ontario, and restricting our analyses in this way allows us to accurately report on the opioid volume dispensed in MME. However, we may be slightly underestimating the true opioid dose dispensed since we are unable to capture other, rarely used opioids in these analyses.

Coroner's Opioid-Related Death Data

We defined opioid-related deaths using data abstracted from the coroners' investigations in Ontario. Although all deaths that are sudden and unexpected or unnatural undergo a coroner's investigation, it is possible that we missed come cases of opioid-related deaths – particularly among the elderly where deaths may be attributed to other causes (e.g. cardiac arrest). Despite this, coroner's data is considered to be a highly valid method for defining drug overdose deaths, and therefore represents a major improvement over research that has historically relied on information obtained from death certificates and large administrative databases.

Impact And Implications Of Findings

INFORMING GUIDELINES AND POLICY DECISION-MAKING

The results of the findings of this work have had considerable implications on drug policy decision-making across North America. In the United States, these studies have been used by the Food and Drug Administration (FDA) and the Department of Transportation in the development of opioid-related policies. Specifically, the FDA used the results of the work related to opioid dose and adverse events to inform post-marketing requirements for long-acting opioids that were introduced in early 2016.[53] Furthermore, in 2014, results from our analysis of the association between opioid dose and risk of injury in a motor vehicle accident were used in a report for the Federal Motor Carrier Safety Administration in the United States Department of Transportation to inform regulations for physical qualifications for commercial drivers.[54] In addition, as described earlier, the United States CDC has cited several of our studies in their recommendations of lower dose thresholds in their 2016 guidelines for opioid use in chronic non-cancer pain.[20]

In Canada, federal leadership on opioid prescribing and overdose has been limited, however the results from this body of research have been used provincially in Ontario to inform a number of opioid-related policies. These include the decision to require prior authorization for reimbursement of OxyNeo on the public drug program[55], and to delist high strength opioid formulations for CNCP beginning in January 2017.[56,57] The results of this work have also been cited extensively by the provincial government in communications related to the release of the Ontario Opioid Strategy.[58-60] Finally, the Canadian guidelines for opioid use in chronic non-cancer pain are currently being revised, and the results of several of these studies are contributing to the evidence base to inform these recommendations. With the announcement of a federal Statement of Action to address the opioid crisis, there is an emerging opportunity for existing opioid research to contribute to this work. In particular, the findings of this thesis are well situated to inform Health Canada's commitments to better informing Canadians about the risks of opioids, supporting better prescribing practices, and improving evidence-based policy decision making.[61]

POLICY EVALUATION

Overall, the findings of our work presented in this thesis also demonstrate the potential for the rapid conduct of observational studies to generate evidence to evaluate drug policy. Two examples of this are our evaluation of Ontario's opioid legislation,

the Narcotics Safety and Awareness Act, on inappropriate opioid prescribing, and studies examining the impact of long-acting oxycodone availability on drug-seeking behaviour across the United States-Canada border.

Our evaluation of the impact of the NSAA and NMS on potentially inappropriate prescribing was communicated broadly through the Ontario Ministry of Health and Long-Term Care. Following the publication of this work, and related calls for enhanced availability of the NMS to clinicians, Ontario announced in November 2016 that they will be working towards expanding access to this database to all physicians in the province.[28] This aligns with prescription monitoring programs across Canada where physicians have real time access to prescription monitoring programs to better inform their prescribing practices.[62]

Furthermore, the findings reported in **Chapter 9** related to potential cross-border movement of generic long-acting oxycodone were presented to the Federal Minister of Health to inform discussions between Canadian and United States government officials. In particular, policy-makers in the United States voiced concerns about the potential for generic, non-tamper deterrent forms of long-acting oxycodone to be diverted across the border and sold illegally. Our study provided evidence to suggest that this did not appear to be occurring through dispensing from retail pharmacies close to these border crossings, although we could not preclude the possibility that generic long-acting oxycodone could be diverted across the border through other means (e.g. thefts from pharmacies or drug manufacturers).

CLINICAL PRACTICE

The implications of this work on clinical practice are broad, and include informing high dose prescribing practices, raising awareness of the risks associated with opioid use for chronic non-cancer pain, and highlighting potentially dangerous combinations of opioids with other substances. For example, in **Chapter 10**, we report a high prevalence of high-dose, long-acting opioid use, despite overall reductions in the rate of opioid prescribing among Ontario's public drug beneficiaries. Given the trend towards lower dose thresholds in clinical practice guidelines over the past year[20], and our findings of considerable harm associated with high dose opioid use[2,3], this provides important information for clinicians as they evaluate their prescribing habits for this class of drugs. Furthermore, this work provides useful baseline data that can be used to evaluate the potential impact of changes in policies and guideline recommendations on clinical practice.

The studies reported in **Chapters 4 and 7** also provide important information for clinicians regarding the potential risks of commonly used substances among opioid users. In particular, although it is well appreciated that alcohol should be avoided among opioid users, our finding that 1 in 5 opioid-related deaths in Ontario involved alcohol, and that the vast majority of these deaths were accidental could help reinforce the importance of these warnings when communicating this risk to patients. Furthermore, our finding of a clinically important, and potentially fatal, interaction between opioids and gabapentin has considerable consequences for clinicians, particularly given our finding that almost 10% of opioid users are also prescribed gabapentin in Ontario. Therefore, it is anticipated that communication of these findings to prescribers in Ontario could help shift prescribing practice for these products, including dose adjustments or drug discontinuation wherever possible.

Future Directions

As the opioid prescribing and drug policy environment continues to shift, there is an ongoing need to continue this research. Core topic areas in need of ongoing research include policy evaluation, patterns of opioid use among the entire Ontario population, and an investigation of an interaction between opioids and pregabalin.

POLICY EVALUATION

In 2016 and early 2017, there have been several shifts in policy and federal engagement in the Canadian opioid public health crisis that have the potential to have an important impact on prescribing, pain management, access to addiction treatment, and risk of overdose. At the national level, this includes both Health Canada's Joint Statement of Action to Address the Opioid Crisis[61] and the impending release of revised clinical practice guidelines for opioid use in chronic non-cancer pain. Provincially, Ontario's opioid strategy includes the delisting of high strength opioid formulations for non-palliative care patients (January 2017) and the October 2016 implementation of a province-wide fentanyl patch-for-patch program, requiring that patients return used fentanyl patches before more can be dispensed from retail pharmacies.[28,56,57] Given the considerable resources being dedicated to these policies and programs, there is a need for ongoing efforts to evaluate their impact to ensure that these resources are being directed towards the most effective interventions. Several of the methods and indicators developed and reported in this thesis can act as baseline data upon which to build these evaluations.

Furthermore, our work also highlights the potential for drug policy to have unintended consequences for patients. For example, there is currently a concern that decreased access to high strength opioid formulations, and increased pressure on physicians to prescribe fewer opioids could lead to opioid-addicted patients being left without access to prescribed medications and poor access to addiction treatment programs. Furthermore, there is concern in the pain community that restrictive opioid prescribing policies could lead to poorly treated pain if alternatives are not provided. Therefore, it is imperative that future research also monitors the impact of new policies and programs on patients to ensure that they do not lead to unintended harm.

EXPANDED GENERALIZABILITY

As described earlier in this chapter, one core limitation to some of the studies described in this thesis is our inability capture opioid prescribing outside of the public drug program in Ontario. This will change in the near future as Ontario has announced its intention to expand access to the Narcotics Monitoring System to support important research in this area. In particular, the NMS was recently linked to the ICES repository, thus allowing researchers to conduct studies that can evaluate the extent of opioid prescribing in this province, and how risks and patient profiles differ across a broad range of demographic and geographic subgroups. This will allow for broad expansion of the generalizability of research findings in Ontario that will have important implications for policy-makers. Priority study questions that should be conducted once linked NMS data are available include: 1) descriptive studies of patient demographics, opioid indication, mental health diagnoses, and health services utilization among opioid users, stratified by age, gender, geography, and socio-economic status; 2) quantification of the potential contribution of diverted and illicit opioids on fatal and non-fatal overdoses; and 3) examination of the association between circumstances of opioid initiation (including volume and formulation dispensed) and risks of long-term use and overdose.

CONCOMITANT USE OF OPIOIDS AND PREGABALIN

Pregabalin and gabapentin are two similar anticonvulsants that are used as adjuncts for the treatment of chronic pain. Given our findings in **Chapter 7** of an important drug-drug interaction between gabapentin and opioids, we suggest that a future study investigates whether a similar interaction exists with

pregabalin. We were unable to examine this association in our study because pregabalin was only recently added to the public drug formulary in Ontario, and so we did not have a sufficient number of exposed cases and controls to study this question. Data in Ontario suggests that patterns of dispensing of these products have shifted towards preferential use of pregabalin over gabapentin[63], highlighting the need for us to assess whether a similar pharmacodynamic interaction exists between opioids and this more commonly prescribed medication.

Conclusions

Opioid dose and related adverse events continue to climb in Ontario, posing a considerable societal burden due to this early loss of life. By 2013, nearly two Ontarians died every day from opioid-related causes, and 1 in 5 of these deaths involved alcohol. The public health importance of this is highlighted by the finding that the number of opioid-related deaths exceeded those attributable to road trauma in Ontario in 2013, and that 1 in 8 deaths among young adults is related to an opioid overdose. Furthermore, the high doses at which opioids are being prescribed to public drug beneficiaries in Ontario will put an increasing number of people at risk of fatal overdose and injuries in motor vehicle accidents. Despite the implementation of a guideline and legislation designed to address this issue, these interventions have had limited impact on prescribing practices and patient risk. Future research is needed to continue to evaluate the impact of Canadian opioid policy on clinical practice and patient outcomes. Furthermore, there is a need for similar research to be conducted in other jurisdictions in Europe and Asia to measure the extent to which prescription opioid overdose is an emerging public health concern. This will help ensure that drug decision-makers have timely access to evidence to inform the efficient diversion of resources to those initiatives most likely to improve patient care and reduce opioid-related harm.

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