

The association between non-concordance with the *Canadian Guideline for Safe and Effective Use of Opioids in Chronic Non-Cancer Pain* and opioid overdose death in Quebec.

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Abstract:

Background: In Canada, the United States of America (U.S.A), and many other regions worldwide, more and more people are dying of prescription opioid analgesic (POA) overdose death. The death rate from POA overdose has quadrupled in the U.S.A. since 1999 and tripled in Ontario. These pharmaceuticals remain useful and important tools in the practice of medicine, although many have suggested changes to prescribing behavior should be among the intervention strategies to curb this epidemic. Canadian physicians wish to minimize overdose and other opioid related-harms while using these medications to optimal clinical effectiveness. To assist physicians in achieving this balance, a national collaboration examined evidence and published the *Canadian Guideline for Safe and Effective use of Opioids in Non-Cancer Pain (CGCNCPP)* in 2010. We retrospectively assessed if non-concordance with prescription characteristic recommendations given in this guideline was predictive of overdose death.

Methods: Using a nested-case control design within the public health insurance cohort of Quebec from 2001-2010, we examined the relationship between death from opioid overdose and dispensed opioid prescriptions non-concordant with recommendations in the *CGCNCPP*. Cases meeting criteria for prescription opioid overdose death were identified through provincial coroner and death certificate data and were restricted to individuals with pharmaceutical insurance from the Régie d'Assurance Maladie du Québec (RAMQ) in the 210 days prior to overdose death. Individuals with an active cancer diagnosis were excluded because of substantial differences in prescribing recommendations in cancer-related pain management. Controls were sampled randomly from time, age, and sex matched individuals in the same cohort and subject to the same inclusion criteria. Non-concordance was assessed through longitudinal analysis of data on prescriptions dispensed in the 180 days prior to case death. We used conditional logistic regression to estimate the magnitude of the relationship between number of non-concordance events and overdose death.

Results: Five hundred people who died of POA overdose while covered by RAMQ pharmaceutical insurance were dispensed at least one POA in the 180 days prior to death, of which 73 had an age, sex, and time-matched control who had also been dispensed at least one

POA in the same period. There were 1,326 dispensed opioid prescriptions among cases, with a total of 375 non-concordant events, and 469 dispensed opioid prescriptions among controls, with a total of 111 non-concordant events. In multivariate analysis, POA overdose death was associated with the number of dispensed benzodiazepine prescriptions (aOR 2.91; 95% CI 1.21-7.00), and opioid prescriptions (aOR 1.20; 95% CI 1.02-1.40), as well as initiating opioid therapy with an extended release formulation (aOR 6.38; 95% CI 1.07-37.94). Total number of non-concordance events was not significantly associated with POA overdose death (aOR 1.03; 95% CI 0.88-1.21).

Interpretation: Increased numbers of dispensed opioid and benzodiazepine prescriptions are important risk factors for POA overdose death in Quebec. Prescription of extended release opioids to opioid naïve patients is significantly associated with increased odds of POA overdose death; prescribers should initiate therapy using immediate release formulations and transition patients to extended release when stable dosing is established. Further study with a larger number of cases is needed to determine whether non-concordance with additional *CGCNCP* recommendations is associated with POA overdose death.

Résumé:

Contexte: Au Canada, aux États-Unis, ainsi que dans plusieurs autres régions à travers le monde, la mortalité liée aux surdoses d'opioïdes d'ordonnance a augmenté rapidement. Le taux de mortalité dû à surdose d'opioïdes d'ordonnance a quadruplé en Amérique depuis 1999 et a triplé en Ontario durant la même période. Les médecins canadiens souhaitent minimiser les surdoses et d'autres méfaits associés avec ces médicaments, tout en utilisant ces médicaments à leur potentiel thérapeutique maximal. Afin d'aider les médecins à atteindre cet équilibre, une collaboration nationale a examiné l'évidence et a publié le *Canadian Guideline for Safe and Effective Use of Opioids in Chronic Non-Cancer Pain (CGCNCPP)* en 2010. Nous avons évalué de manière rétrospective si la non-concordance des prescriptions avec les recommandations émises par le *CGCNCPP* prédisait le décès par surdose.

Méthodologie: Nous avons utilisé une modèle d'étude cas-témoins; les cas viennent de la cohorte des bénéficiaires de la Régie d'assurance de maladies du Québec (RAMQ) entre 2001 et 2010. Les cas qui remplissaient les critères pour une surdose d'opioïdes d'ordonnance ont été identifiés par le bureau du coronar du Québec et par les certificats de décès et ont été restreint aux individus participants au régime d'assurance médicaments de la RAMQ pendant les 210 jours précédant le date de décès. Les individus avec un diagnostic de cancer ont été exclus en raison des différences considérables entre les recommandations pour les ordonnances pour la gestion de la douleur liée au cancer. Les témoins ont été sélectionnés au hasard des individus de la même cohorte qui étaient appariés selon le sexe, l'âge et qui étaient vivants le jour de décès du cas apparié. Les témoins ont été soumis aux mêmes critères d'inclusion que les cas. Nous avons mesuré la non-concordance en effectuant une analyse longitudinale des données d'ordonnances émises pendant les 180 jours avant le décès. Nous avons utilisé une régression logistique conditionnelle pour mesurer l'association entre non-concordance et mortalité.

Résultats: Cinq cent victimes de surdose qui étaient bénéficiaires d'assurance médicaments de la RAMQ avaient été distribuées au moins une ordonnance d'opioïdes dans les 180 jours précédant leurs décès. De celles-ci, 73 avaient un témoin apparié qui avait aussi été distribuée au moins une ordonnance d'opioïdes dans la même période. Il y avait 1,326 prescriptions distribuées

pour des opioïdes chez les cas, comprenant une totale de 375 instances de non-concordance, et 469 prescriptions distribué pour des opioïdes parmi les témoins, comprenant une totale de 111 instances de non-concordance. Dans l'analyse multivariée, le décès suite à la surdose a été associée avec le nombre d'ordonnance de benzodiazépines distribués (aOR 2.91; 95% CI 1.21-7.00), et le nombre d'ordonnance d'opioïdes (aOR 1.20; 95% CI 1.02-1.40), ainsi que l'initiation de thérapie en utilisant d'opioïdes à action prolongée (aOR 6.38; 95% CI 1.07-37.94). Le nombre total d'instances de non-concordance n'était pas associé de manière significative avec les décès lié à la surdose d'opioïdes d'ordonnance (aOR 1.03; 95% CI 0.88-1.21).

Interprétation: L'augmentation de nombre d'ordonnances d'opioïdes et de benzodiazépines constituent des facteurs de risques importants pour le décès suite à une surdose au Québec. L'initiation de la thérapie avec les opioïdes à action prolongée augmente de manière significative les chances de décès suite à une surdose. Les prescripteurs devraient initier la thérapie en utilisant des opioïdes à action immédiate et passer aux opioïdes à action prolongé quand le dosage c'est stabilisé. Des futures études comprenant un nombre plus grand de cas sont nécessaire pour déterminer si la non-concordance avec les autres recommandations de *CGCNCP* sont associé aux surdoses d'opioïdes d'ordonnance.

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Contributions of Authors

Dr. Colleen Fuller, first author, contributed collaboratively to study conception and design, conducted a literature review, derived prescription recommendations from guidelines, completed data analysis, and wrote the manuscript with incorporation of revisions from the other authors. Dr. David Buckeridge and Dr. Luc de Montigny conceived of the larger investigation into overdose deaths of which this study formed a part, and obtained approval and the required data, provided methodological guidance, and contributed to review and revision of the manuscript.

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Chapter 1: Introduction

Background and Rationale

After two hundred years of use in Western medicine and thousands more in other cultures, opioid medications remain one of the most complex and contentious aspects of medicine. Their ongoing use has been a controversial issue influenced by medicine, science, grass-roots advocates, religion, industry, crime, and politics. Societies have long sought to find the balance of maximizing the benefits of pain relief opioids can provide while minimizing the myriad of harmful effects they can provoke. Patterns of use, pain conditions, and external influences have changed considerably over time, and today, in Western cultures, have brought the issue to a state where neither the maximum benefit nor the minimum harms are being achieved – a state of crisis.

Prescription opioid analgesic (POA) overdose death rates have escalated dramatically over the last two decades in many regions around the world.^{1–5} In 2010, 16,651 people died of prescription opioid overdose in the United States of America, representing an increase of more than 400% from 4,030 such deaths in 1999.⁶ Deaths attributable to prescription opioid medications have surpassed the number of deaths from heroin and cocaine combined and exceed deaths from homicide (16,259 deaths in 2010) and drowning (3,782 deaths in 2010).^{7–9} These figures do not include deaths from injury such as traffic collision where opioid intoxication was a contributing cause. In Canada, there has been a similarly large increase in the number of people dying of overdose; the province of Ontario saw a doubling in the opioid overdose death rate between 1991 and 2004,² with 325 such deaths in 2009 alone.¹⁰ In 2010, this provincial death rate rose to 3.5 times that of 1991, with 549 deaths.¹¹ Opioid mortality surveillance is conducted sporadically and with varying methods on a provincial level in Canada, impeding precise documentation of national trends; however, there is evidence to suggest similarly high rates of prescription opioid overdose in other provinces.^{10,12,13} In the U.S.A., where surveillance of this health issue is coordinated at a federal level, the Centers for Disease Control and Prevention (CDC) have declared an epidemic of POA overdose.^{8,14}

The dramatic rise in mortality from prescription opioid overdose is one tragic aspect of the cumulative individual and societal harms that have been associated with this class of pharmaceutical. POAs have been implicated in morbidity from addiction, infectious diseases, physical injury, hyperalgesia, mental health disorders, and economic losses.^{10,15} These harms also require significant use of health care resources; the CDC estimates that for every prescription opioid overdose death there are 35 emergency department visits directly related to opioid misuse or abuse.¹⁴

There is ample ecologic and individual-level evidence that increased rates of morbidity and mortality from POAs reflect increased rates of prescribing and total dosages prescribed.^{2,5,13,16–21} Despite these harms, opioid medications are tremendously useful tools in treating patients with severe and unremitting pain and it is possible that the boom in population-level consumption may reflect improvement in previously undertreated pain conditions, particularly cancer pain and chronic non-cancer pain.^{22–25} Even so, evidence from Denmark, a country similar to Canada in regards to chronic pain epidemiology, suggests the prevalence of chronic pain has been stable from 2000 to 2005.²⁶ Although all stakeholders can likely find common ground in the desire for efficacious pain relief without risk of addiction, overdose, or other harms, the reality is a highly polarized state of uncertainty, complicated by influences from both pharmaceutical industry and criminal drug diversion.^{27–31} The work of physicians, seeking to best help patients with pain in need of relief while respecting the principle of *primum non nocere* (first do no harm) for both their own patients and the greater community they serve, is undoubtedly a challenging undertaking.

Clinicians, regulatory colleges, policy makers, and public health agencies are using a combination of approaches to try to mitigate POA-related harms. These approaches include: identifying patients at high risk for opioid-related harms for closer monitoring, improving access to addiction treatment, providing education to patients regarding risk, concurrently prescribing the opioid-antidote naloxone with opioids or providing it through community programs, introducing prescription drug monitoring programs, improving medical education regarding

pain management, and involving law enforcement institutions in preventing and addressing illicit use.^{32–37}

Researchers studying POA overdoses and related harms have commonly concluded that changing clinician prescribing practices should be a key component in intervening in the evolution of this epidemic.^{2,38,39} This recommendation is based on the observation that many of the individuals who misuse or overdose on POAs obtained these drugs by their own prescription or that of a friend or family member.^{10,40,41} There have been calls for both the introduction of universal prescribing precautions and targeted precautions for high risk individuals, but evidence is needed to determine if these strategies are likely to be effective.^{32,42} Several guidelines for pain management and opioid prescribing have been released in an effort to aid clinicians in decision-making.^{32,43–50} In the context of limited evidence and divergent opinions, it is not clear whether these guidelines will have the desired impact. This thesis will contribute to the body of evidence regarding this intervention strategy by retrospectively evaluating whether non-concordance with the opioid prescribing recommendations of a recent Canadian guideline (*The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain*) is associated with opioid overdose death in Quebec.

Chapter 2: Literature Review

Risk factors for prescription opioid analgesic overdose

The increasing rates of death and harm from prescription opioids have led to a surge of research aimed at identifying individual-level risk factors for opioid overdose. The results of these investigations consistently reveal heterogeneity amongst victims of overdose, although some important clusters have been identified.¹³

The greatest burden of POA overdose death is consistently among those in their forties and fifties; however, there is a significant incidence at all adult ages.^{5,12,51–53} Males are typically overrepresented compared to females, although this gender difference is most pronounced at younger ages (i.e., 15–24 years),^{5,14} and the rate of death in women has been escalating more rapidly than in men.^{8,19} Amongst Americans, rates are highest in white Americans compared to

rates among people of other ethnic backgrounds.^{14,51,54} Other factors that have been associated with higher risk include: rural place of dwelling, concurrent use of benzodiazepines or alcohol, number of opioid prescriptions received, number of prescribers, number of pharmacies used, high prescribed opioid doses, a history of substance abuse, and a history of mental health disorder (including depression).^{13,16,21,40,51,52,55–58} A 2014 Tennessee study showed that 55% of POA overdose deaths were preceded by one or more of three risk factors: high number of prescribers, high number of pharmacies used, and high mean dose.¹⁶

Alongside the search for individual level risk factors, a number of studies have examined community level risk factors. These studies have consistently shown higher rates of death in geographic areas and medical practices where there are higher levels of prescribing.^{13,18,39,52} There have been mixed results for the utility of prescription monitoring programs as a protective factor,^{13,37} although community naloxone distribution and training programs do seem to be protective.⁵⁹

The clinical utility and complexity of opioid use

Although there is a clear burden of individual and societal morbidity and mortality associated with prescription opioids, there are also obvious benefits to the continued medical use of these pharmaceuticals. Prescription opioids are a widely used and critical form of analgesia that enable surgical interventions, relief from acute severe pain (such as following a bone fracture), and effective and humane palliative care^{25,45}. Notably, they have been regarded as a standard tool of practice in alleviating cancer-related pain for many years.²⁵ More recently, numerous clinician and patient groups have advocated strongly and successfully for more liberal use of opioids as treatment for chronic non-cancer pain (CNCP).³¹ Chronic non-cancer pain (commonly defined as pain of duration greater than 3 months) affects approximately 19-29% of people in Canada and similar developed nations, although the prevalence is slightly lower (16%) in the province of Quebec.^{22,60,61} CNCP is not a single medical syndrome, but rather a common symptom of many conditions: mechanical back pain, neck pain, osteoarthritis of the knee and

chronic headaches are among the most common types of CNCP treated with opioid medications.^{22,62}

Although advocacy for improved relief of CNCP has stimulated a remarkable amount of investigation into the efficacy of opioid treatment, the scientific evidence provides weak support at best that this class of medication is efficacious in select pathologies and, importantly, highlights the substantial adverse events associated with long-term POA use.^{32,63–65}

Balancing the risks and benefits of prescription opioid use for CNCP treatment is a contentious issue with considerable variation in modern medical practice and medical training.

Nevertheless, CNCP has come to be the dominant indication for opioid prescriptions – in 1999 opioids dispensed for CNCP treatment accounted for 86% of all opioid sales in the U.S.A.²⁷ More recent studies have also indirectly indicated that CNCP accounts for the majority of opioids prescribed.^{60,62,66–68} Additionally, an observational study in Utah, U.S.A. showed the prevalence of CNCP amongst decedents of opioid overdose was much higher (88.6%) than typical in the general population. In this same group of decedents, 80.2% had received a prescription for an opioid, by far the most common way of obtaining the medication, in the year prior to death.⁴⁰

Taken together, these findings suggest there is potential to prevent opioid overdoses through changes to clinical practice, specifically in the management of chronic non-cancer pain.

Sources of prescription opioids

There is good reason to believe that judicious prescribing of opioids according to best-practice guidelines may help to reduce the burden of opioid overdose. A recent study from Ontario, Canada, showed 56.1% of opioid overdose decedents had been prescribed an opioid in the month prior to death and 81.9% in the 12 months prior.² In this same study, post-mortem toxicology results identified oxycodone in 66.7% of cases who had been dispensed oxycodone after their most recent physician visit. Other researchers have found that similarly high proportions of decedents (40.5-87.4%) had been prescribed an opioid medication in various periods within one year prior to death.^{40,69,70}

Diversion of opioids intended for medical use is another important route by which people obtain access to these pharmaceuticals. However, this observation does not necessarily imply that the POA overdose deaths among these individuals could not be prevented through shifts in prescribing patterns. Numerous studies have shown that the majority of non-medically used opioids (i.e., opioids not prescribed to the person consuming the drug, whatever the intent of the consumer) are taken with the intent to alleviate pain and are obtained from a family member or friend who themselves obtained the medication by prescription.^{30,69,71–73} In a 2012 American national survey of the general population, 54% of people who had used an opioid not prescribed to them had obtained the medication most recently for free from a family member or friend, and an additional 14.9% had paid a family member or friend for the drug. Of these friends and family members, 85.8% had obtained the opioid by prescription.⁴¹ Interviews with family members of 222 overdose decedents in Utah indicated 54% of these individuals had obtained opioid medications from a friend or relative for free and 36% from the same sources for payment.⁴⁰ Purchase from a drug dealer was more common in this group of decedents than amongst the general populations mentioned above (25% vs 4.3%). Still, even this source has connections back to medical care; drug dealers themselves frequently obtain the POAs they sell by obtaining a prescription for themselves or for a “sponsored” individual.²⁸ Although there is little prescribers can do to directly prevent diversion, there is an argument to be made that cautious prescribing, adherence to guidelines and improved patient education may contribute alongside other interventions to limit the amount of opioids available for dispersal through these routes.

Another important consideration in studying POA overdose is not just where the opioids are sourced, but why. As discussed earlier, most individuals using the medications with or without their own prescription are seeking pain relief, but some users instead seek the euphoric effects of these medications. Prescription opioid medications have also been frequently implicated in suicidal overdoses, though the majority of POA overdose deaths are unintentional.^{9,12,53,74} Perhaps because of this association, or perhaps to minimize complexity, many researchers restrict their investigation of POA overdose to unintentional deaths. This restriction implies

that the potential for intervention does not exist in the case of deaths from suicide. Although patients do not always divulge plans for intentional death, mental health evaluation is an important aspect of clinical encounters, particularly in the context of chronic pain, and many individuals do openly discuss suicidal ideation. As the majority of opioids are accessed via prescription, there is the possibility of intervention at the point of prescription, even in these cases, through exemplary and comprehensive medical care and perhaps universal precautions.

Prescription guidelines as a possible intervention strategy

Numerous pain management and opioid prescribing guidelines have been produced with various objectives and aimed at numerous pain conditions and clinical situations. Notably, in 2010, the *Canadian Guideline for the Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (CGCNCP)*³² was released by a collaboration of health practitioners and endorsed by all of the regulatory colleges of physicians and surgeons in Canada. This guideline specifically targets Canadian medical practice and is comprised of 25 recommendations pertinent to a range of activities from clinical assessment to interdisciplinary collaboration. This resource is specific to opioid use in CNCP management and seeks to enable appropriate use of prescribed opioid medications for pain management while preventing the iatrogenic sequelae of misuse, adverse effects, abuse, addiction, diversion, and overdose. The extent to which these guidelines are likely to achieve these goals is not altogether clear.

In order for POA prescribing guidelines to reduce opioid overdose, the recommendations they provide must be effective and they must also be implemented. Several investigators have attempted to qualify the characteristics of a guideline that encourage it to be implemented or to impact the quality of medical care, although it remains a complex question. Unsurprisingly, guidelines that are supported by strong evidence are more likely to be implemented.^{75,76} A strong evidence base, however, is by no means the only requirement, which is fortunate in the case of opioid prescribing for CNCP, given the relative paucity of such evidence. Guidelines written in precise, concrete language, that are quantifiable, consistent with existing standards of care, and require no additional resources or changes to routines are also more effective in

eliciting the desired outcome.⁷⁵⁻⁷⁸ Many of the recommendations of the *CGCNCP*, in particular those pertaining to the characteristics of prescriptions such as dosing frequency and quantity, are consistent with these highly implementable features. Further, a recent systematic review of the *CGCNCP* along with 12 other recent guidelines for opioid use in CNCP found remarkable consistency between the recommendations of all guidelines.⁷⁹ Within the social context of support from Canadian medical regulatory authorities, the *CGCNCP* appears to be the best positioned among opioid prescribing guidelines to effectively mitigate opioid-related harms, including overdose, in Quebec.

The study conducted for this thesis adds to the current body of evidence around prescription opioid overdose prevention through a retrospective evaluation of the association between non-concordance with prescribing recommendations provided by the *CGCNCP* and prescription opioid overdose in the province of Quebec.

Chapter 3: Manuscript

The following manuscript will be submitted for publication to the Canadian Medical Association Journal and has been formatted according to the specifications of this journal.

The association between non-concordance with the *Canadian Guideline for Safe and Effective Use of Opioids in Non-Cancer Pain* and opioid overdose death in Quebec.

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Abstract

Background: The rate of death due to overdose of prescription opioid analgesics (POAs) has increased alarmingly in Canada. Canadian physicians wish to minimize overdose and other opioid-related harms while responsibly using opiates to optimal clinical effectiveness. To assist physician decision-making in opioid prescribing, a national collaboration of health professionals published the *Canadian Guideline for Safe and Effective Use of Opioids in Non-Cancer Pain (CGCNCP)* in 2010. We retrospectively assessed whether non-concordance with these prescription recommendations was predictive of overdose death.

Methods: We used a nested case-control design within registrants to the Quebec public health insurance from 2001-2010. Cases were identified through provincial coroner and death certificate data and restricted to individuals covered by the public pharmaceutical plan with no active cancer diagnoses who had been dispensed at least one POA within 180 days prior to death. Controls were sampled randomly from time, age, and sex matched individuals in the same cohort and subject to the same inclusion criteria. Non-concordance with *CGCNCP* recommendations was assessed by longitudinal analysis of prescription dispensation data. The association between non-concordance events and prescription opioid overdose death was evaluated using conditional logistic regression, adjusting for urban dwelling, number of prescribers, and number of dispensed prescriptions for opioids and for benzodiazepines. Subgroup analyses stratified by indication of intent of death were performed. Individual recommendations were analyzed in the same manner.

Results: Five hundred people who died of POA overdose while covered by RAMQ pharmaceutical insurance were dispensed at least one POA in the 180 days prior to death; 73 of these cases had an age, sex, and time-matched control who had also been dispensed at least one POA in the same period. There were 1,326 dispensed opioid prescriptions among cases, with a total of 375 non-concordant events, and 469 dispensed opioid prescriptions among controls, with a total of 111 non-concordant events. In multivariate analysis, POA overdose death was associated with the number of dispensed benzodiazepine prescriptions (aOR 2.91;

95% CI 1.21-7.00), and opioid prescriptions (aOR 1.20; 95% CI 1.02-1.40), as well as initiating an opioid naïve patient on an extended release formulation (aOR 6.38; 95% CI 1.07-37.94). The total number of non-concordance events was not significantly associated with POA overdose death (aOR 1.03; 95% CI 0.88-1.21).

Interpretation:

Increased numbers of dispensed opioid and benzodiazepine prescriptions are important risk factors for POA overdose death in Quebec. Prescription of extended release opioids to opioid naïve patients is significantly associated with increased odds of POA overdose death; prescribers should initiate therapy using immediate release formulations and transition patients to extended release when stable dosing is established. Further study with a larger number of cases is needed to determine whether non-concordance with additional *CGCNCP* recommendations is associated with POA overdose death.

Introduction

Prescription opioid analgesic (POA) misuse, abuse, and overdose are important public health issues as an escalating number of premature deaths are associated with or caused by prescription opioids.^{51,80} In addition to increased mortality, there is significant morbidity among users of prescription opioids and those around them through mechanisms of addiction and addiction recovery;¹⁰ injury (such as traffic collisions or falls in the elderly);^{17,81,82} infectious diseases;⁸³ societal costs of drug diversion and trafficking; economic losses to communities;⁸⁴ and comorbid mental health concerns.^{85,86} The issue is especially compelling due to the iatrogenic aspect, with rates of harms rising in tandem with rates of prescription, implicating medical professionals involuntarily in the chain of events culminating in the genesis of an epidemic.^{2,16,17,87} A lack of sufficient evidence to guide practice and a critical need for improved treatment of pain, particularly chronic pain, has led the medical community to search aggressively for strategies to minimize POA-related harm without sacrificing the ability to treat pain conditions.

Increasingly, opioid analgesic prescription guidelines are being developed to help clinicians balance the potential harms and benefits of treating patients with opioid medications.^{32,43,47–50,88} Such intervention at the point of prescribing may be an effective strategy – research in Ontario (Canada) showed 82% of opioid overdose decedents had had at least one opioid prescription in the 12 months preceding their death (the median number of prescriptions was 10).² As chronic non-cancer pain has been viewed as a main driver of the escalation in POA use and availability,²⁷ guidelines may be especially practical in this domain.

In 2010, a national group of health professionals (including family physicians, pain and addiction medicine specialists, and pharmacists), endorsed by a collaboration of all of the provincial and territorial colleges of physicians and surgeons in Canada, published the *Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (CGCNCPP)*.³² This document provides a comprehensive series of recommendations for an approach to opioid use in chronic pain care. The guideline includes several specific recommendations regarding opioid

prescribing. Our research assessed whether non-concordance with the prescribing recommendations in this guideline was predictive of death from POA overdose.

Methods

Design

We used a nested case-control design, aiming for full capture of all cases of prescription opioid overdose death in the province of Quebec from Jan 1, 2001 to Dec 31, 2010. The study protocol and data request was approved by the *Commission d'accès à l'information* of Quebec and was funded by a grant from the Canadian Institutes of Health Research.

Data Sources

Bureau du coroner du Québec (BCQ)

The coroner's office is responsible for investigating all accidental or unexpected deaths in the province, and maintains records on causes of death and substances found through toxicological testing.

Institute de statistique du Québec (ISQ)

The ISQ is the source of vital statistics, including death certificate information (containing causes of death), for the complete population of Quebec.

Régie d'Assurance Maladie du Québec (RAMQ)

The RAMQ administers both universal health care insurance for all residents of Quebec and public pharmaceutical insurance for beneficiaries of employment assistance (15%), employed individuals without private health care benefits and their dependents (53%), and those aged 65 years or older (32%), together comprising approximately 43% of the total provincial population.⁸⁹ Health-care utilisation data and records of dispensed pharmaceuticals to outpatients were obtained from this source.

Case and control selection

Study participants were drawn from a province-wide database of overdose deaths between Jan. 1, 2001 and Dec. 31, 2010, which had been previously assembled for a broader, ongoing study regarding overdose patterns in Quebec. This database was created through collaboration of the three data sources listed above. The BCQ first identified all cases meeting cause of death or post-mortem toxicology criteria (Appendix I). These cases were linked by the ISQ to death certificate data, which identified additional cases using ICD-10 codes (Appendix I) for overdoses as primary and secondary causes of death. This set of cases was then communicated to the RAMQ, which used risk-set sampling to select age and sex matched controls at a ratio of 10:1 from the cohort of all adults enrolled in the provincial health insurance program alive at the date of the case index event. Health care utilisation information from Jan.1, 2000 to Dec. 31, 2010 was extracted by the RAMQ for all cases and controls. All participants were given a unique identifying number and personal identifying information was removed. This final data set was then communicated by the RAMQ to the research team.

From this set of potential participants, we included only cases with an identified primary or secondary cause of death due to intoxication by at least one POA, or having at least one POA found at post-mortem toxicology during coroner assessment (Appendix II). All cases and controls were required to have continuous enrollment in the RAMQ pharmaceutical insurance coverage program for the 210 days prior to the case event in order to enable ascertainment of exposure events. Because of substantive differences in opioid prescribing for cancer-related pain, cases and controls with a cancer diagnosis within 365 days prior to the case event date were identified using diagnostic codes (Appendix II) and excluded. In order to target the effect of prescription non-concordance, only cases and their corresponding controls who had at least one opioid prescription dispensed in the 180 days prior to case event were used for final conditional regression analyses.

Exposure assessment: non-concordance with *CGCNCP* prescription characteristic recommendations.

The complete *CGCNCP* was examined for recommendations meeting the following criteria:

- 1) The action is specific to prescription characteristics (e.g., dose, duration, formulation).
- 2) The action is the responsibility of the prescriber.
- 3) The recommended action has a clear, objective and quantifiable interpretation.
- 4) The action is reasonably aimed at reducing the risk of overdose (vs. other harms such as constipation).
- 5) A determination of non-concordance can be derived from RAMQ pharmaceutical dispensing data.

This assessment resulted in thirteen distinct recommendations (Appendix III). Of these, four recommendations applied to all opioid prescriptions, three only to therapy-initiating prescriptions, two to dose-increasing prescriptions, one to prescriptions changing from immediate to extended release formulations, and three to prescriptions switching the class of opioid used. Some recommendations varied further depending on the age of the patient (ie: >75y vs not) and concurrent use of benzodiazepines. Where the *CGCNCP* provided a range of doses (e.g., 5-10mg every six hours), the maximum allowable dose was used as the cutoff for non-concordance (i.e., more than 10mg every six hours). When the *CGCNCP* gave a time range before a dose increase (e.g., 2-5 days), the minimum recommended duration was used as the cutoff for non-concordance (i.e. dose increased before two days elapsed). Exposure events were ascertained using RAMQ dispensed prescription data. Concurrent benzodiazepine use was derived from the same source. A prescription was determined to be therapy-initiating if no opioid was dispensed in the 30 days prior to the 180 day study window. Due to complexity, only the seven recommendations applicable to all prescriptions and opioid-initiating prescriptions were evaluated for this study. The total number of non-concordance events per individual and number of non-concordance events for each specific recommendation per individual were tabulated in the 180 days prior to case event. Non-concordance events were hypothesized to lead to an opportunity for opioid overdose by leading to increased dose or potency of opioids available to the patient. The number of prescribers, pharmacies, opioid prescriptions and benzodiazepine prescriptions in the 180 days prior to case event were obtained from RAMQ dispensed prescription data.

We did not differentiate between prescriptions for acute and chronic non-cancer pain for several reasons:

- 1) Treatment indication is not captured by the RAMQ; therefore, any attempt to differentiate acute from chronic pain would be highly subjective and potentially result in misclassification.
- 2) Outpatient opioid prescribing guidelines for acute pain are scarce but, where they exist, are generally consistent with those for chronic non-cancer pain.^{49,50,90}
- 3) The suspected mechanism of potential harm is common despite pain type.
- 4) Acute pain requiring higher doses of opioids than recommended under *CGCNCP* are most likely treated in hospital; this investigation is limited to outpatient prescriptions.
- 5) CNCP is considered to be the primary area where POAs are used.²⁷

Statistical Analysis:

Data were analyzed using R software version 3.0.3 (<http://www.r-project.org/>).

The association between POA overdose death and number of prescription non-concordance events was assessed using conditional logistic regression, adjusting for number of prescribers, number of dispensed opioid prescriptions, urban dwelling, and number of dispensed benzodiazepine prescriptions in the study window. Subgroup analyses were stratified by intentional, unintentional and undetermined death. The same analysis method was used for the number of non-concordant events for individual recommendations.

Results

Of the 1,268 cases of POA overdose death identified as meeting initial inclusion criteria (having RAMQ pharmaceutical insurance and no cancer diagnosis), 500 cases (39.4%) had been dispensed at least one opioid medication in the 180 days (6 months) prior to death and were eligible to be included in the study. Of these cases, 73 had an age and sex matched control alive at the time of the case index date, who had also been dispensed at least one opioid medication in the 180 days prior to the date of death of their matched case. A flowchart showing the

derivation of the study sample is shown in Figure 1. Just over half (52.1%) of cases were women, and mean age was 52.6 years with a range of 23.1-86.4. Among the cases, 89.0% lived in a urban area at the time of death and 74.6% of controls were urban-dwelling. Further descriptive characteristics for the cases are presented in Table 1. A total of 1,326 individual opioid prescriptions were dispensed to the 73 cases and 469 to the 73 controls during the study window. Descriptive characteristics of the prescriptions dispensed to the matched cases and controls are presented in Table 2. A comparison of the same characteristics in the 73 matched cases and 427 unmatched cases is available in Appendix IV.

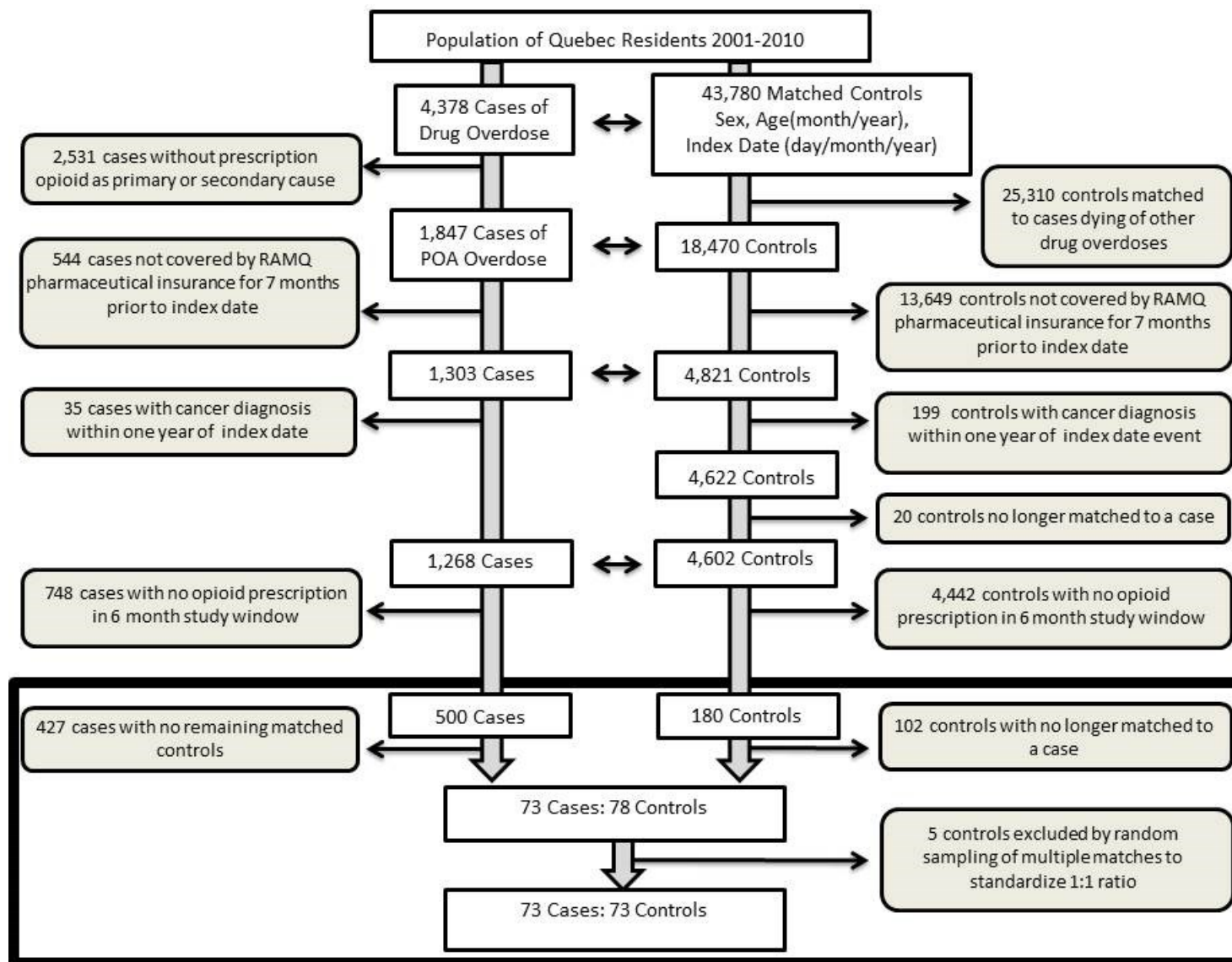


Figure 1: Derivation of study population. The box outlined in black indicates the level of population of interest; cases known to have been dispensed an opioid prior to overdose. An unknown proportion of the 544 cases without RAMQ pharmaceutical insurance would also be candidates for intervention through implementation of *CGCNCP* recommendations.

Table 1: Descriptive characteristics of cases

Characteristic	Cases (n=73)
Age: <i>mean (range)</i>	52.6 (23.1-86.4)
Female Sex: <i>no. (%)</i>	38 (52.1%)
Urban dwelling: <i>no. (%)</i>	65 (89.0%)
<i>Manner of Death no. (%)</i>	
Unintentional Death	31 (42.5%)
Intentional Death	28 (38.4%)
Undetermined Intent	11 (15.1%)
Missing	3 (4.1%)
<i>Drugs found at toxicological testing no. (%)</i>	
	*
Codeine	11 (15.1%)
Fentanyl	6 (8.2%)
Hydromorphone	25 (34.2%)
Meperidine	1 (1.4%)
Methadone	8 (11.0%)
Morphine	12 (16.4%)
Oxycodone	20 (27.4%)
Other	11 (15.1%)
Unspecified	35 (47.9%)
Benzodiazepine (any)	27 (37.0%)
<i>Year of death no. (%)</i>	
2001	1 (1.4%)
2002	4 (5.5%)
2003	2 (2.7%)
2004	3 (4.1%)
2005	7 (9.6%)
2006	9 (12.3%)
2007	6 (8.2%)
2008	15 (20.1%)
2009	12 (16.4%)
2010	14 (19.2%)

*3 cases missing data, 6 no opioid, 22 single opioid, 42 multiple opioids

Table 2: Descriptive characteristics of study participants and dispensed prescriptions

Prescription Characteristics	Cases (n=73)	Controls (n=73)	OR (95% CI)
Opioid prescriptions dispensed: <i>total; mean (range)</i>	1,326; 18.2 (1-243)	469; 6.4 (1-116)	1.06 (1.01-1.10)
1	7	32	
2-5	19	22	
6-10	14	9	
11-15	10	4	
≥16	23	6	
Physicians providing opioid prescriptions: <i>mean (range)</i>	1.82 (1-15)	1.40 (1-3)	1.37 (0.96-1.96)
1	48	52	
2	10	13	
3	10	8	
≥4	5	0	
Pharmacies dispensing opioids: <i>mean (range)</i>	1.58 (1-21)	1.15 (1-3)	2.00 (0.96-4.15)
1	56	63	
2	10	9	
3	6	1	
≥4	1	0	
Total oral grams ME* dispensed per person†: <i>mean (range)</i>	19.46 (0.11-97.50)	8.09 (0.01-97.20)	1.03 (1.01-1.06)
Benzodiazepine prescriptions dispensed: <i>total, mean (range)</i>	585; 8.0 (0-78)	45; 0.6 (0-27)	1.77 (1.11-2.83)
0	39	68	
1-5	4	2	
6-10	12	2	
11-15	6	0	
≥16	12	1	
Number of prescriptions per opioid: total (% of dispensed opioid prescriptions)			
Codeine	30 (2.3%)	12 (2.6%)	1.21 (0.86-1.72)
Fentanyl	80 (6.0%)	56 (11.9%)	1.04 (0.93-1.16)
Hydromorphone	616 (46.5%)	86 (18.3%)	1.14 (1.03-1.26)
Meperidine	14 (1.1%)	11 (2.3%)	1.05(0.73-1.50)
Methadone	0 (0%)	9 (1.9%)	---
Morphine	152 (11.5%)	97 (20.7%)	1.01 (0.97-1.06)
Oxycodone	430 (32.4%)	197 (42.0%)	1.02 (0.99-1.05)
Other opioid	4 (0.3%)	1 (0.2%)	1.54 (0.42-5.61)

*Morphine equivalent. †Does not include dispensed prescriptions for which morphine equivalency is not reliably established (ex. tramadol, methadone).

Evaluation of prescription non-concordance revealed a total of 375 non-concordance events among cases, and 111 among controls. Two recommendations were so rarely non-concordant as to inhibit their individual analysis: the prohibition of parenteral opioid formulations (zero non-concordance events), and the recommendation not to use fentanyl in initiating opioid management (1 event among cases, 1 event among controls). Number of pharmacies used was not adjusted for in the multivariate analysis as it was highly correlated with number of prescribers. Results of univariate and multivariate analyses are presented in Table 3. For analyses stratified by intent (intentional, unintentional and undetermined) see Appendix V. POA overdose death was associated with the number of dispensed benzodiazepine prescriptions (aOR 2.91; 95% CI 1.21-7.00), and opioid prescriptions (aOR 1.20; 95% CI 1.02-1.40), as well as initiating opioid therapy using an extended release formulation (aOR 6.38; 95% CI 1.07-37.94). The total number of non-concordance events was not significantly associated with POA overdose death (aOR 1.03; 95% CI 0.88-1.21).

Table 3: Calculated odds ratios (OR) and adjusted odds ratios (aOR) for covariates and non-concordance event counts for individual recommendations and as total count. Adjusted for number of opioid prescriptions, urban dwelling, number of prescribers and number of benzodiazepine prescriptions. For an explanation of the recommendations see Appendix III.

Covariate	Cases (n=73)	Controls (n=73)	Univariate OR (95% CI)	R2	R3	Multivariate analysis aOR (95% CI)			Total events	All rules
	mean (range)	mean (range)				R4	R6	R7		
Number prescribers	1.82 (1-15)	1.40 (1-3)	1.37 (0.96-1.96)	0.77 (0.41-1.45)	0.82 (0.43-1.54)	0.79 (0.42-1.45)	0.70 (0.35-1.39)	0.63 (0.31-1.24)	0.80 (0.43-1.49)	0.62 (0.29-1.35)
Number of pharmacies	1.68 (1-21)	1.15 (1-3)	2.00 (0.96-4.15)	NA	NA	NA	NA	NA	NA	NA
Number of benzodiazepine prescriptions	8.0 (0-78)	0.6 (0-27)	1.77 (1.11-2.83)	2.19 (1.20-4.01)	2.06 (1.13-3.77)	2.29 (1.12-4.66)	2.58 (1.30-5.10)	2.42 (1.28-4.54)	2.05 (1.11-3.77)	2.91 (1.21-7.00)
Number of opioid prescriptions	18.2 (1-243)	6.4 (1-116)	1.06 (1.01-1.10)	1.11 (1.01-1.22)	1.09 (0.99-1.21)	1.13 (1.00-1.28)	1.17 (1.03-1.31)	1.15 (1.03-1.27)	1.09 (0.97-1.23)	1.20 (1.02-1.40)
Urban dwelling	65 (89.0%)	53 (75.7%)*	2.43 (1.01-5.86)	3.61 (0.75-17.46)	4.33 (0.97-19.29)	4.05 (0.87-18.87)	3.17 (0.66-15.24)	3.90 (0.83-18.34)	4.73 (0.95-23.51)	2.30 (0.41-12.86)
All prescriptions	# events (# cases)	# events (# controls)								
R1 Parenteral route	0 (0)	0 (0)	NA							NA
R2 Meperidine used	14 (4)	11 (6)	1.05 (0.73-1.50)	0.54 (0.07-4.25)						0.76 (0.27-2.15)
R3 Multiple opioids used	113 (6)	10 (3)	1.78 (0.62-5.14)		1.25 (0.47-3.34)					1.25 (0.17-9.50)
R4 Max dose exceeded	204 (22)	55 (8)	1.10 (1.00-1.21)			0.97 (0.83-1.13)				0.96 (0.80-1.15)
Opioid-initiating prescriptions	# events (# cases)	# events (# controls)								
R5 Fentanyl used	1 (1)	1 (1)	NA							NA
R6 Extended release used	18 (17)	9 (5)	1.64 (0.82-3.28)				7.89 (1.45-43.04)			6.38 (1.07-37.94)
R7 Dose exceeded	25 (21)	25 (20)	1.00 (0.61-1.63)					2.47 (0.88-6.89)		1.65 (0.58-4.68)
Total non-concordance events	375 (49)	111 (37)	1.12 (1.02-1.23)						1.03 (0.88-1.21)	

*2 control subjects missing residence data

Interpretation

Between 2001 and 2010, a total of 1,847 people died of POA overdose in Quebec, representing a death rate of approximately 245 per million population over ten years. The percentage of POA overdose decedents who had been dispensed a prescription opioid preceding their death was somewhat lower in our population (39.4%) than found in the literature.^{40,69,70,91} This result may reflect underlying differences in the populations receiving public pharmaceutical insurance or in the prescribing patterns in Quebec compared to other regions.⁹² The proportion of female decedents in our study is also somewhat higher than in other studies.² A temporal trend similar to that in the U.S.A. emerged with higher numbers of decedents in the later years of the decade.

Our results revealed a high number of deaths involving hydromorphone or oxycodone relative to the other opioids. These were also the most common opioids to have been prescribed among cases, accounting for 1,046 of their 1,326 (78.9%) opioid prescriptions. For oxycodone, this finding is consistent with other studies,^{1,2} however, hydromorphone is over-represented compared to other research in both regards.^{19,91} This result may indicate regional or temporal variation in prescribing patterns, or reflect differences in hydromorphone availability in different districts.

We also found a considerable presence of benzodiazepines as a concurrent toxin on coroner investigation and as a concurrently prescribed substance in the period preceding death. Further, the number of dispensed benzodiazepine prescriptions was strongly and significantly associated with POA overdose death, with relative odds of death increasing an estimated 2.91 times for each additional benzodiazepine prescription. This association has previously been revealed⁹³ and suggests that interventions in the POA overdose epidemic should target benzodiazepine use patterns to a similar degree as those of opioids.

Level of non-concordance with CGCNCP

Our results are also indicative of the practice patterns of Quebec prescribers in the decade prior to the release of the *CGCNCP*. The number of non-concordance events varied greatly for different recommendations. For example, we found no instances of parenterally administered

drugs but found 259 instances of daily doses exceeding 200 milligrams morphine equivalent (MME). The publication and implementation of the *CGCNCP* in 2010 may have led to increased concordance with all recommendations our results can serve as a point of reference for future evaluation of practice patterns. It is noteworthy that more than half of both cases and controls were dispensed a prescription that was non-concordant with at least one guideline recommendation, indicating these measures were not universally in use in Quebec at this time.

Association of non-concordance events with overdose death

Unlike other studies, we did not find the number of prescribers nor the number of pharmacies used to be clearly associated with overdose death, which may indicate that the practice of “doctor shopping” is less common in Quebec, or reflect regional differences in delivery of primary care givers. Estimates of these effects may also have been limited by our sample size. The total number of opioid prescriptions dispensed, however, did show a relative increase in odds of death of 1.20 times for each additional prescription (6.19 times for every 10 additional prescriptions).

In unadjusted analysis, the main exposure of interest, total non-concordance events, was associated with increased odds of death by 1.12 times for each additional non-concordance event. However, in the multivariate analysis, there was no association between increased total number of non-concordance events in the 180 days prior to index date and opioid overdose death. Many individuals were dispensed non-concordant prescriptions as identical renewals. Thus, if some non-concordance events have a greater potential to cause an effect at its first event than with repetition (for example, due to individual tolerance of a dose higher than 200MME/day), this may explain the lack of significant effect here. It may also be that the limited sample size inhibited detection of an important difference here.

Limitations & Strengths

It is important to note that the *CGCNCP* is a comprehensive set of 25 recommendations ranging from appropriate medical interview to screening for drug abuse to the prescription characteristics discussed in this work. Although implementation of the complete set of tools

may prevent POA-related harm by other means, evaluating non-concordance with the entirety of the recommendations would not be possible within the resources available for this research. Additionally, there may be some circumstances captured in our study population where acute pain conditions, and possibly missed cancer diagnoses, would lead to prescriptions where the recommendations would not be expected to be applied. We also note the uncertain generalizability of our results to those with private drug insurance, as previous research in Quebec has shown differences in medication adherence may exist between these two groups, depending on the medication class.^{94–96} Other notable groups not captured in this study are those prescribed opioids paid for via worker's compensation or automobile insurance, Aboriginal peoples (who receive alternate pharmaceutical coverage), and those living in long-term care centres. Our control sampling strategy restricted our sample size and may have compromised overall study power; this work should be repeated with a larger sample size. Nevertheless, cases included in the study are similar in characteristics to those unmatched (Appendix IV) suggesting little potential for bias to have been introduced in this process. Finally, a consistent limitation across studies in this field, including this one, is the inability to account for opioid medications obtained through diversion or other illicit means, although it is clear from previous research this is a considerable concern.⁶⁹ Such exposures may be an important source of unmeasured confounding.

Despite these limitations, our research brings several strengths to the current body of work in this field. Much of the current literature is from uncontrolled, observational study and survey data. Our study was able to target those individuals receiving opioid prescriptions to compare the effect of a proposed intervention between population-representative controls and POA overdose decedents. An important strength is the comprehensive strategy we used to optimize case detection, using linked coroner and death certificate data over a 10 year period in a large population. Our work also benefited from objective measures of guideline non-concordance through use of administrative and pharmaceutical data, which has been shown to be highly accurate in previous research.⁹⁷ These non-concordance measures were reflective of the

diversity of opioid use in real-world practice and provide valuable evidence for clinical guidelines and practice.

Implications for Practice, Policy, and Research

Increased number of prescriptions for opioids, benzodiazepines, and initiation of opioid therapy with long-acting formulations are all associated with increased odds of overdose death.

Measures targeting reduction of benzodiazepine use patterns and abuse independent of opioid treatment may be an important opportunity for intervention in opioid overdose deaths. Further research is required to determine whether the additional recommendations given by the *CGCNCP* are likely be effective in limiting POA overdose. Routine inclusion of treatment indication for prescription would enable researchers to produce higher quality evidence in this area.

Chapter 4: Limitations, Lessons, and Strengths

All epidemiologic studies will have areas of weakness and strength and these provide insights to apply to future research. There are likewise some limitations to acknowledge of the evidence presented here. Perhaps most prominent among these is the restriction to sample size that resulted from the control sampling strategy. Due to time and funding constraints, this study was conceived and carried out using data from a set of time, sex and age matched cases and controls that had been assembled for a different, albeit similar, study. When the inclusion criteria of this study were applied, 500 cases of prescription opioid overdose deaths were eligible for the study. Ideally, matched controls would have been sampled at this stage from among those in the RAMQ cohort that met the same inclusion criteria, allowing all 500 eligible cases to be used for the analysis. Unfortunately this could not be accomplished with the resources available, and only 73 cases had retained a matched control meeting all inclusion criteria. This speaks to the need for meticulous planning in order to use all available information to produce the highest quality epidemiological evidence – a lesson in experience that has been duly learned. Despite this limitation, the results of the analysis of this subset of cases contribute to current knowledge and may be built upon in the future by further analysis of the entire group of eligible cases if appropriate controls can be obtained.

Another important limitation comes from the fact that the indication for pharmaceutical treatment is neither required, nor routinely collected as a part of RAMQ pharmaceutical insurance data. Thus, investigators using this data source must frequently infer treatment indications from diagnostic codes. This imprecise process may well introduce bias into the results. In this study, we used diagnostic codes to exclude individuals with a cancer diagnosis in the 365 days preceding the case index date in order to exclude non-concordance evaluation of opioid prescriptions intended for cancer-related pain. Although we believe this criterion is reasonable for study population derivation, we cannot be completely certain that none of the 1,795 POA prescriptions given to the 146 individuals evaluated were for cancer-related pain. If a significant number of prescriptions were in fact indicated for cancer-related pain, this could lead to misclassification of the exposure (non-concordance events) and perhaps bias the study results.

Similarly, POAs are also frequently prescribed for acute pain (for example, post-surgical pain). Because this study used only administrative data, we could not reliably differentiate between such instances and those of chronic non-cancer pain. Any process for doing so would be highly subjective and probable to result in misclassification. Consider the illustrative example of an individual with chronic pain due to degenerative disc disease (DDD) of the back and osteoarthritis of the knee who takes 6mg of hydromorphone per day for pain relief. Imagine this individual undergoes spinal surgery for their DDD, spends seven post-operative days in hospital using a patient-controlled analgesia IV pump and fills a new prescription on the date of discharge for 40mg of morphine per day. Even by reviewing the medical records of this patient containing this detailed information, it is difficult to make an accurate determination as to whether the morphine prescription is indicated for the chronic knee pain, the chronic back pain, or the acute post-surgical pain. To attempt to make such determinations using administrative data would be considerably more difficult and likely to result in significant misclassification. Despite this limitation, there is consistency between outpatient opioid prescription guidelines for acute pain management and the recommendations of the *CGCNCP*,^{49,50} and the suspected mechanisms of effect in overdose deaths (higher doses or potency of opioids leading to sedation and respiratory depression) are common to both clinical situations. Thus, we believe it is justifiable to assess all outpatient prescriptions in patients without cancer for non-concordance with the *CGCNCP*, acknowledging that some of these prescriptions may be for acute pain conditions.

The generalizability of this study is somewhat limited by uncertainty in the degree to which opioid prescription data in the publicly insured cohort reflect similar practices amongst the privately and alternately insured. This issue is discussed in more detail in the manuscript portion of this thesis (Chapter 3).

Despite the limitations discussed, this research has several notable strengths. Firstly, we were able to optimize capture of opioid overdose cases by using coroner data and toxicology results in addition to death certificate results over a period of ten years. Additionally, a considerable

amount of the literature in this field is from observational or survey data. The nested case-control design used here allows a stronger causal implication of the association between non-concordance with recommendations and opioid overdose death than would an observational study.

This study is also notable for its setting of the province of Quebec. This is important as much of the scientific research around opioid overdose is conducted in regions of the United States of America, and most of the Canadian information has come from the province of Ontario. As discussed in the introductory chapters of this thesis, the epidemiology of prescription opioid overdose is complex and liable to be affected by regional differences in legal milieu, medical practice patterns, pharmaceutical advertising and lobbying, population pain patterns, accessibility of health services, illicit drug use availability and preferences of non-medical prescription opioid users. By conducting this study in the Quebec context, our results allow a more complete understanding of the burden of POA overdose in Canada, and provide a comparison point for other provinces.

Chapter 5: Summary of Findings and Future Directions

Our study further confirmed the strong association between POA overdose and the number of benzodiazepine prescriptions dispensed to an individual, and importantly, this relationship was found while assessing POA prescribing recommendations which adjust for concurrent benzodiazepine use. This association suggests that effective prevention of POA overdoses may also require specific interventions to reduce benzodiazepine use beyond POA dosing adjustments. This association may be due to the sedative effects both classes of drugs are known to have and reflect a synergistic physiologic effect. It might also suggest a common profile of physical and mental health comorbidities. Prescribers should use increased caution when prescribing these medications concurrently and avoid these combinations when possible. There may also be an important role for pharmacists in evaluating the medication profile of patients and providing counselling to patients as well as feedback to prescribers regarding combination of benzodiazepine and POA medications.

We also found an association between POA overdose and the initiation of opioid therapy using an extended release formulation, supporting the *CGCNCP* recommendation that prescribers should instead initiate therapy with immediate release formulations. We did not find an association between the total number of prescription non-concordance events and POA deaths; however, the work should be extended to all of the 13 derived recommendations before concluding the absence of a relationship. This future work should seek appropriate controls for the entire group of 500 cases who had received a prescription in the 180 days prior to their death in order to improve the precision of effect estimates. Investigators might also consider evaluating the association of non-prescription aspects of the *CGCNCP* and opioid overdose death.

This study also gives some information regarding the degree of concordance with the *CGCNCP* recommendations during the decade preceding their publication. Future work may benefit from our results as a reference point in assessing the implementation of this guideline.

Although there are many avenues of future study in this domain, the knowledge base could perhaps best be advanced through improving the conditions of administrative data collection, upon which such work is commonly based. Specifically, data pertaining to overdose should be

systematically collected and surveilled across Canada in order to more clearly evaluate the burden of this problem. Required inclusion of the indication for opioid treatment (and of any prescribed therapy) would significantly improve the ability to conduct high quality research using administrative data. Finally, investigation into alternative modes of chronic pain management and improved prevention of events and conditions that ultimately lead to chronic pain may also be important in reducing the burden of POA overdose death and should continue to be pursued.

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Appendices

Appendix I: Case ascertainment criteria by BCQ[†] and ISQ[‡] for initial source population

Selection Criteria	Description	Code(s)*
Primary cause of death [‡] [ICD-10]	Poisoning by and exposure to	
	Non-opioid analgesics, antipyretics and anti-rheumatics	X40 X60 Y10
	antiepileptic, sedative-hypnotic, anti-parkinsonism and psychotropic drugs, not elsewhere classified	X41 X61 Y11
	narcotics and psychodysleptics [hallucinogens], not elsewhere classified	X42 X62 Y12
	other drugs acting on the autonomic nervous system	X43 X63 Y13
	other and unspecified drugs, medicaments and biological substances	X44 X64 Y14
Secondary cause of death [‡] [ICD-10]	Poisoning by narcotics and psychodysleptics [hallucinogens], including	
	opium	T40.0
	heroin	T40.1
	other opioids	T40.2
	methadone	T40.3
	other synthetic narcotic	T40.4
	cocaine	T40.5
	other and unspecified narcotics	T40.6
	cannabis (derivatives)	T40.7
	lysergide [LSD]	T40.8
	other and unspecified psychodysleptics	T40.9
Substance found in blood [†] [BCQ EXA_TYPE]	Prescription medication	
	methadone	D711
	alphaprodine	M701
	anileridine	M702
	codeine	M703
	hydrocodone	M705
	hydromorphone	M706
	levorphanol	M708
	meperidine	M709
	morphine	M712
	oxycodone	M714
	pentazocine	M715
	phenazocine	M716
	propoxyphene	M717
	fentanyl	M718
	oxymorphone	M719
	ethoheptazine	M720
	opioid (unspecified)	M721
	Street drug	
	cannabis	D005
	heroin	D704
	mescaline	D710
	amphetamines	D751
	MDMA	D757

methamphetamine	D758
cocaine	D952
phencyclidine	D953
GHB	D958
ketamine	M201

* Accidental poisonings: X40-X44 | Intentional poisonings: X60-X64 | Poisonings of undetermined intent: Y10-Y14

Appendix II: Study inclusion and exclusion criteria:

Case Inclusion Criteria	Code/Description
Primary or secondary cause of death [ICD-10] [‡]	T40.0,T40.2,T40.3,T40.4,T40.6, X42, X62, Y12
Substance found in blood [BCQ EXA_TYPE] [‡]	D711, M701, M702, M703, M705, M706, M708, M709, M712, M714, M715, M716, M717, M718, M719, M720, M721

Case and Control Inclusion Criteria	Code/Description
RAMQ pharmaceutical plan [§]	PA – Personne âgée PS – Prestataire d'assistance-emploi AD - Adhérent AL – Personne admissible au programme d'achat de places

Case and Control Exclusion Criteria	Code/Description
Any cancer diagnosis in year preceding case event [ICD-10, ICD-9]	C00 to C43 [¶] , C45 to C97 140 to 172 ^{**} , 174 to 208

[§] continuous enrollment over 210 days months prior to case event

[¶] ICD-10 C44 non-melanoma skin cancers omitted

^{**} CD-9 173 non-melanoma skin cancers omitted

Appendix III: Prescription recommendations derived from *CGCNCP*

[illegible]

Derived recommendation	Specific doses and time periods	CGCNCP recommendation number
9. Daily dose should not increase by more than recommended amount	<i>For patients under 75 years of age, with no concomitant use of benzodiazepines</i> Codeine IR - 30mg Codeine CR - 50mg Tramadol IR - any up to max dose Tramadol XR: 1. Zytram -any up to max dose 2. Tridural -any up to max dose 3. Ralivia -any up to max dose Morphine IR - 10mg Morphine CR - 10mg Oxycodone IR - 5mg Oxycodone CR - 10mg Hydromorphone IR - 2mg Hydromorphone CR - 4mg Other: No specific recommendations given	R9
	<i>For patients 75 years of age or greater, OR with concomitant use of benzodiazepines</i> Codeine IR - 15mg Codeine CR - 25mg Tramadol IR any up to max dose Tramadol XR: 1. Zytram--any up to max dose 2. Tridural--any up to max dose 3. Ralivia--any up to max dose Morphine IR - 10mg Morphine CR - 10mg Oxycodone IR - 5mg Oxycodone CR - 10mg Hydromorphone IR - 2mg Hydromorphone CR - 4mg Other: No specific recommendations given	R6,R9,R17

Derived recommendation	Specific doses and time periods	CGCNCP recommendation number
<i>Applicable to opioid formulation switches[§]</i>		
10. The patient should be taking the minimum indicated IR daily dose prior to a switch to the XR form of the medication.	Codeine - 100mg Tramadol - 112.5mg Morphine - 20mg Oxycodone - 20mg Hydromorphone - 6mg Other: No specific recommendations given	R9
<i>Applicable to opioid switches[¶]</i>		
<i>a. Switch to fentanyl from codeine</i>		
11. Do not switch from codeine to fentanyl regardless of codeine dose	NA	R8
<i>b. Switch to fentanyl from opioid other than codeine</i>		
12. Daily dose should be at least 60 MME prior to switch	NA	R8
13a. The daily dose should be 75% or less of the MME of the prior opioid	NA	R13
<i>c. Other opioid switches</i>		
13b. The daily dose should be 75% or less of the MME of the prior opioid	NA	R13

*IR denote immediate release; CR denotes controlled release; XR denotes extended release

†New prescription: an opioid prescription with no other active opioid prescription in the 30 days prior to dispensing date.

‡Dose change: an opioid prescription for the same named opioid as a prescription dispensed in the previous 30 days, where the daily dose of the current prescription has changed from the previous.

§Opioid formulation switch: an opioid prescription for the same named opioid as a prescription dispensed in the previous 30 days, but where the formulation has changed from IR to XR or CR (example: morphine IR to morphine CR)

¶Opioid switch: an opioid prescription for a different named opioid than dispensed in the last 30 days (example: morphine to fentanyl).

Appendix IVa: Comparison of characteristics of matched and unmatched cases:

Characteristic	Matched Cases (n=73)	Unmatched Cases (n=427)	p-value *
Age: mean (range)	52.6 (23.1-86.4)	47.2(21.3-93.6)	0.0004
Female Sex: no. (%)	38 (52.1%)	181 (42.4%)	0.132
Urban region: no. (%)	65 (89%)	348 (83.3%)†	0.148
Manner of Death no. (%)			
Unintentional Death	31 (42.5%)	182 (42.7%)	0.980
Intentional Death	28 (38.4%)	176 (41.2%)	0.646
Undetermined Intent	11 (15.1%)	58 (13.6%)	0.744
Missing	3 (4.1%)	11 (2.6%)	0.535
Drugs found at toxicological testing no. (%)			
	‡	§	
Codeine	11 (15.1%)	61 (14.3%)	0.824
Fentanyl	6 (8.2%)	25 (5.6%)	0.475
Hydromorphone	25 (34.2%)	139 (32.6%)	0.712
Meperidine	1 (1.4%)	13 (3.0%)	0.310
Methadone	8 (11.0%)	30 (7.0%)	0.299
Morphine	12 (16.4%)	96 (22.5%)	0.237
Oxycodone	20 (27.4%)	117 (27.4%)	0.940
Other	11 (15.1%)	39 (9.1%)	0.191
Unspecified	35 (47.9%)	183 (42.9%)	0.357
Benzodiazepine (any)	27 (37.0%)	301 (70.5%)	<0.0001
Year of death no. (%)			
			¶
2001	1 (1.4%)	19 (4.4%)	0.066
2002	4 (5.5%)	14 (3.3%)	
2003	2 (2.7%)	25 (5.9%)	
2004	3 (4.1%)	42 (9.8%)	
2005	7 (9.6%)	39 (9.1%)	
2006	9 (12.3%)	45 (10.5%)	
2007	6 (8.2%)	49 (11.5%)	
2008	15 (20.1%)	71 (16.6%)	
2009	12 (16.4%)	69 (16.2%)	
2010	14 (19.2%)	54 (12.6%)	

*t-test statistic. †9 missing postal code data. ‡3 missing data, 6 no opioid, 22 single opioid, 42 multiple opioids.

§ 14 missing data, 47 no opioid, 172 single opioid, 267 multiple opioids. ¶Wilcoxon rank sum test statistic

Appendix IVb: Comparison of prescription characteristics of matched and unmatched cases:

Prescription Characteristics:	Matched Cases (n=73)	Unmatched Cases (n=427)	p-value*
Opioid prescriptions dispensed: <i>total; mean (range)</i>	1,326; 18.2 (1-243)	6,392; 15.0 (1-208)	0.495
1	7	57	
2-5	19	110	
6-10	14	88	
11-15	10	54	
≥16	23	118	
Physicians providing opioid prescriptions: <i>mean (range)</i>	1.82 (1-15)	1.92 (1-17)	0.066
1	48	220	
2	10	110	
3	10	56	
≥4	5	41	
Pharmacies dispensing opioids: <i>mean (range)</i>	1.58 (1-21)	1.48(1-9)	0.147
1	56	288	
2	10	95	
3	6	31	
≥4	1	13	
Total oral grams ME [†] dispensed per person [‡] : <i>mean (range)</i>	19.46 (0.11-97.50)	2.45 (0.01-173.16)	<0.0001
Benzodiazepine prescriptions dispensed: <i>total, mean (range)</i>	585; 8.0 (0-78)	2,721; 6.4 (0-236)	0.178
0	39	251	
1-5	4	13	
6-10	12	7	
11-15	6	8	
≥16	12	148	
Number of prescriptions per opioid: <i>total (% of dispensed opioid prescriptions)</i>			
Codeine	30 (2.3%)	228 (3.6%)	0.358
Fentanyl	80 (6.0%)	253 (4.0%)	0.828
Hydromorphone	616 (46.5%)	3119 (48.8%)	0.913
Meperidine	14 (1.1%)	163 (2.6%)	0.892
Methadone	0 (0%)	23 (0.4%)	0.355
Morphine	152 (11.5%)	913 (14.3%)	0.254
Oxycodone	430 (32.4%)	1638 (25.6%)	0.275
Other opioid	4 (0.3%)	55 (0.9%)	0.679

*Wilcoxon rank sum test statistic. †Morphine equivalent. ‡Does not include dispensed prescriptions for which morphine equivalency is not reliably established (ex. tramadol, methadone).

Appendix Va: Calculated odds ratios (OR) and adjusted odds ratios (aOR) for covariates and non-concordance event counts for individual recommendations and as total count, among deaths deemed unintentional. Adjusted for number of opioid prescriptions, urban dwelling, and number of prescribers.

Covariate	Cases (n=31)	Controls (n=31)	Univariate OR (95% CI)	R2	R3	Multivariate analysis aOR (95% CI)			Total events	All rules
	mean (range)	mean (range)				R4	R6	R7		
Number prescribers	2.13 (1-15)	1.35 (1-3)	1.81 (0.90-3.64)	1.70 (0.72-4.01)	NA	1.72 (0.57-5.22)	1.65 (0.71-3.87)	1.94 (0.74-5.09)	1.74 (0.59-5.16)	2.18 (0.55-8.56)
Number of pharmacies	2.16 (1-21)	1.13 (1-2)	4.53 (1.14-17.84)	NA	NA	NA	NA	NA	NA	NA
Number of benzodiazepine prescriptions	10.6 (0-78)	1.1 (0-27)	2.97 (0.54-16.30)	NA	NA	NA	NA	NA	NA	NA
Number of opioid prescriptions	25.4 (1-243)	8.3 (1-116)	1.03 (0.99-1.07)	1.02 (0.98-1.06)	NA	1.01 (0.97-1.05)	1.02 (0.98-1.06)	1.02 (0.98-1.06)	1.01 (0.97-1.05)	1.00 (0.97-1.04)
Urban dwelling	26 (84.0%)	19 (63.3%)*	2.50 (0.78-7.97)	3.38 (0.74-15.36)	NA	3.64 (0.88-15.13)	3.60 (0.88-14.74)	4.01 (0.91-17.71)	3.74 (0.91-15.45)	4.04 (0.72-22.54)
All prescriptions	# events (# cases)	# events (# controls)								
R1 Parenteral route	0 (0)	0 (0)	NA							NA
R2 Meperidine used	13 (3)	9 (4)	1.07 (0.74-1.55)	1.03 (0.55-1.91)						0.89 (0.39-2.04)
R3 Multiple opioids used	99 (3)	8 (1)	NA		NA					NA
R4 Max dose exceeded	95 (8)	14 (3)	1.15 (0.95-1.39)			1.15 (0.91-1.46)				1.13 (0.90-1.43)
Opioid-initiating prescriptions	# events (# cases)	# events (# controls)								
R5 Fentanyl used	0 (0)	0 (0)	NA							NA
R6 Extended release used	5 (5)	5 (3)	1.00 (0.38-2.66)				0.75 (0.35-2.26)			1.14 (0.25-5.15)
R7 Dose exceeded	9 (3)	11 (4)	0.71 (0.30-1.65)					0.48 (0.16-1.45)		0.46 (0.11-1.88)
Total non-concordance events	221 (19)	49 (19)	1.12 (0.97-1.30)						1.10 (0.94-1.30)	

*1 control missing residence data

Appendix Vb: Calculated odds ratios (OR) and adjusted odds ratios (aOR) for covariates and non-concordance event counts for individual recommendations and as total count, among deaths deemed intentional. Adjusted for number of opioid prescriptions, urban dwelling, and number of prescribers.

Covariate	Cases (n=28)	Controls (n=28)	Univariate OR (95% CI)	R2	R3	Multivariate analysis aOR (95% CI)			Total events	All rules	
	mean (range)	mean (range)				R4	R6	R7			
Number prescribers	1.68 (1-6)	1.50 (1-3)	1.19 (0.70-2.03)	0.80 (0.40-1.63)	0.60 (0.26-1.43)	0.80 (0.39-1.63)	0.67 (0.28-1.58)	0.74 (0.35-1.59)	0.80 (0.39-1.63)	0.39 (0.11-1.43)	
Number of pharmacies	1.18 (1-3)	1.25 (1-3)	0.71 (0.22-2.28)	NA	NA	NA	NA	NA	NA	NA	
Number of benzodiazepine prescriptions	5.32 (0-28)	0 (0-0)	22.9 (0 - inf)	NA	NA	NA	NA	NA	NA	NA	
Number of opioid prescriptions	11.18 (1-55)	5.93 (1-30)	1.06 (0.99-1.14)	1.07 (0.98-1.17)	1.09 (0.99-1.20)	1.08 (0.96-1.21)	1.12 (1.01-1.25)	1.09 (0.99-1.19)	1.05 (0.96-1.15)	1.18 (0.98-1.42)	
Urban dwelling	25 (89.3%)	23 (82.1%)	1.67 (0.40-6.97)	1.35 (0.26-6.96)	2.08 (0.35-12.47)	1.23 (0.16-9.26)	0.38 (0.05-2.79)	0.75 (0.12-4.62)	2.03 (0.27-14.98)	0.32 (0.01-11.02)	
All prescriptions	# events (# cases)	# events (# controls)									
R1 Parenteral route	0 (0)	0 (0)	NA								
R2 Meperidine used	1 (1)	2 (2)	0.5 (0.05-5.51)	1.11 (0.07-17.64)						0.66 (0.00-682.53)	
R3 Multiple opioids used	6 (2)	2 (2)	1.53 (0.52-4.44)	2.25 (0.67-7.60)						2.70 (0.28-26.06)	
R4 Max dose exceeded	9 (8)	2 (1)	1.04 (0.93-1.17)			0.99 (0.82-1.19)					0.99 (0.76-1.29)
Opioid-initiating prescriptions	# events (# cases)	# events (# controls)									
R5 Fentanyl used	1 (1)	1 (1)	NA			NA					NA
R6 Extended release used	5 (5)	5 (3)	1.00 (0.38-2.66)			7.48 (1.15-48.52)					7.88 (1.00-62.40)
R7 Dose exceeded	12 (8)	5 (4)	1.90 (0.73-4.98)					2.37 (0.87-7.18)			2.12 (0.63-7.16)
Total non-concordance events	91 (20)	47 (12)	1.08 (0.95-1.24)							1.08 (0.89-1.30)	

Appendix Vc: Calculated odds ratios (OR) for covariates and non-concordance event counts for individual recommendations and as total count, among deaths of undetermined intent. Adjusted odds ratios could not be calculated due to restricted sample size.

Covariate	Cases (n=11)	Controls (n=11)	Univariate OR (95% CI)
	<i>mean (range)</i>	<i>mean (range)</i>	
Number prescribers	1.55 (1-5)	1.00 (1-1)	NA (0-inf)
Number of pharmacies	1.09 (1-2)	1.00 (1-1)	NA (0-inf))
Number of benzodiazepine prescriptions	9.27 (0-26)	0.91 (0-7)	1.43 (0.87-2.34)
Number of opioid prescriptions	19.45 (1-56)	3.27 (1-13)	NA (0-inf)
Urban dwelling	11 (100%)	9 (81.8%)	NA (0-inf)
All prescriptions	# events (# cases)	# events (# controls)	
R1 Parenteral route	0 (0)	0 (0)	NA
R2 Meperidine used	0 (0)	0 (0)	NA
R3 Multiple opioids used	8 (1)	0 (0)	NA
R4 Max dose exceeded	46 (4)	6 (1)	1.64 (0.45-6.02)
Opioid-initiating prescriptions	# events (# cases)	# events (# controls)	
R5 Fentanyl used	0 (0)	0 (0)	NA
R6 Extended release used	3 (3)	2 (1)	1.34 (0.29-6.14)
R7 Dose exceeded	3 (3)	5 (2)	0.66 (0.18-2.42)
Total non- concordance events	60 (8)	13 (5)	1.26 (0.86-1.83)