Opioid Prescribing Patterns and Prolonged Opioid Use in Opioid-Naive Adults after Surgical and Emergency Care in Nova Scotia

by

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DEDICATION

I dedicate this thesis to anyone who has lost a loved one too soon to opioids. Especially parents, and those whose loved ones' opioid problem began with a prescription for acute pain.

I also dedicate this thesis to those who have been deprived of effective pain relief after surgery or injury due to broad policies that could not account for individual needs.

To all of you, with humility, I would like to say: we care.

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ABSTRACT

Opioid prescribing for acute pain remains a cornerstone of pain management in acute care settings in Canada. There is evidence that opioid use for prolonged periods (i.e., for three months or longer) is associated with higher risk of opioid-related harms compared to only short-term use. I present in this thesis three component studies that investigate prescribing patterns to opioid naive adults who fill opioid prescriptions after receiving surgical and emergency care in Nova Scotia, Canada, risk of prolonged opioid use, and risk factors associated with prolonged use.

In a systematic review of global evidence about opioid naive adults, I found that risk of prolonged use was 6% (95% CI 4% - 9%) after opioid use following surgical care, 9% (95% CI 6% – 12%) after emergency care, and 3% (95% CI 2% - 6%) after dental care. I also identified with 'high' certainty, the following as potentially important risk factors for prolonged use: a medical history of arthritis, anxiety, depression, or drug abuse in the previous year, and being of Black race; with 'moderate' certainty: a medical history of back pain, neck pain, alcohol abuse, or tobacco use in the previous year. The evidence about first prescription days' supply and dose was limited and rated to be of 'very low' to 'low' certainty.

In a cross-sectional population-level study of opioid naive adults who filled opioid prescriptions in community pharmacies within 14 days of surgical or emergency care in Nova Scotia between April 2017 and March 2019, I found that among 36,716 subjects included in the study, hydromorphone, overall, was the most frequently prescribed opioid formulation followed by codeine. Median days' supply of filled prescriptions was 3 (IQR2-5) and 50 MME/day (IQR 30-75) was the median daily dose. I also found that 10.9% of prescriptions were >7 days' supply and 20.2% were ≥90 MME/day These patterns of prescribing varied across settings and, for the surgical population, across provider specialty groups even after adjusting for patient characteristics.

In a retrospective cohort study (n=27,665), I estimated that overall risk of prolonged opioid use in Nova Scotia was 3.5%. In an analysis adjusting for patient characteristics and additional opioid fills during the first week, I found that risk of prolonged use was higher for patients who filled first-prescriptions that were longer in days' supply or for long-acting opioids. I observed an interaction between days' supply and dose of first-prescription, and found that higher average daily dose was associated with higher predicted probability of prolonged use when prescriptions were for 7 and 14 days, but not 3 days' supply.

Overall, the results from the three component studies improve our understanding of opioid prescribing to opioid naive adults in acute care settings in Nova Scotia and risk of prolonged use locally and globally. The results may be useful for physicians, patients, clinical guideline development, public health professionals, and policymakers when interpreted in context of benefits, risk of other opioid-related harms, as well as patients' values and preferences.

LIST OF ABBREVIATIONS USED

aOR	adjusted odds ratio
CCI	Canadian Classification of Health Interventions
CCP	Canadian Classification of Procedures
CDC	Centres for Disease Control
CI	confidence interval
CIHI	Canadian Institute of Health Information
DAD	Discharge Abstract Database
DINs	drug information numbers
DIS	Drug Information System
DWH	Nova Scotia Department of Health and Wellness
ED	emergency department
EHR	electronic health record
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HDNS	Health Data Nova Scotia
ICD	International Classification of Diseases
IQR	interquartile range
MASTER	Insured Patient Registry
MME	morphine milligram equivalents
MME	morphine milligram equivalents
MSI	Medical Services Insurance
NACRS	National Ambulatory Care Reporting System
OR	odds ratio
POQI-4	American Society for Enhanced Recovery and Perioperative Quality Initiative
US	United States
VITAL	Vital Statistics

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1 Chapter One: Introduction

1.1 Overview

Prescription opioids are a main contributor to the opioid epidemic that Canada currently faces.[1,2] Common indications for receiving opioid prescriptions are acute pain conditions related to surgery or injury, or more general emergency-related pain.[3-5] In the year 2018, 8% of the adult Canadian population filled opioid prescriptions while opioid-naive at the time.[6] When opioids are deemed necessary and appropriate for the treatment of acute pain, opioid naivety creates a unique opportunity for safe, short-term prescribing where the potential harms associated with long-term opioid therapy[7] can be avoided. However, recent evidence from the United States (US) and Canada has shown that around 4% of patients who were previously opioid-naive and filled opioid prescriptions after surgical and emergency care were still using opioids six months later (i.e., had transitioned to prolonged opioid use).[8-10]

Despite the growing body of literature aiming to determine risk of prolonged opioid use and important risk factors for opioid-naive populations across acute care settings like the emergency department and surgical settings, findings are inconsistent. [9-12] Furthermore, no quantitative synthesis of existing data or assessment of overall certainty in existing evidence in a systematic review focused on this population was identified at the time that the thesis protocol was developed. Synthesized evidence is important to determine the scope of the problem and to identify factors and prescribing patterns that are consistently associated with higher risk of prolonged use. Furthermore, no identified previous studies considered whether certain prescribing patterns may interact with each other to differently affect the risk of prolonged use in opioid-naive populations, despite

evidence that various combinations of dose and length of treatment modify the risk of developing opioid use disorder in patients with chronic non-cancer pain.[13]

Excessive prescribing to patients receiving opioid prescriptions after surgical and emergency care has been identified as a problem in Canada and the United States.[14,15] However, little is known about opioid prescribing patterns to opioid-naive populations with acute pain in Nova Scotia. For the general pain population in Canada, variations in opioid prescribing patterns across provinces have been observed[16], indicating that extrapolation of findings across jurisdictions may not be appropriate. Furthermore, within jurisdictions and institutions, some of the factors identified as contributing to variation in length and dose of prescriptions – potentially important contributors to harms – included prescriber characteristics.[17-20] Variations in prescribing by setting and provider specialty may reflect the potential influence that shared clinical and training experiences among physician groups may have on prescribing decisions. However, little is known about whether such variations exist in Canada.

The lack of synthesized global evidence and local data about patterns of prescribing and risk of prolonged opioid use interferes with efforts to improve the safety of opioid prescribing to opioid-naive populations presenting to acute care settings with acute pain. Lack of synthesized evidence also makes it more challenging to recommend interventions and develop tailored clinical practice guidelines to reduce harms, including unintended prolonged use. Relative to chronic pain populations and populations on long-term opioid therapy, opioid-naive populations with acute pain have been studied much less. This thesis presents three component studies that aim to contribute to the existing evidence

about this understudied population and to inform policy, clinical practice, and future research in this area.

1.2 Opioid class of medications

Opioids, commonly referred to as narcotics, are a chemically related class of pain relief medications used to treat acute pain, such as injury- and surgical-related pain, as well as chronic cancer- and non-cancer-related pain. Prescription opioids are classified as Schedule I drugs under the Controlled Drugs and Substances Act (CDSA) in Canada. Their use is lawful when prescribed by licensed practitioners and used by the person for whom the prescription was written.[21] Prescribed opioids include hydrocodone (Tussionex®, Vicoprofen®), hydromorphone (Dilaudid®), oxycodone (oxyNEO®, Percocet®, Oxycocet®, Percodan®), tramadol (Ultram®, Tramacet®, Tridural®, Durela®), morphine (Doloral®, Statex®, M.O.S®), codeine (Tylenol®2,3,4, i.e. codeine plus acetaminophen), fentanyl patches and others.

Prescription opioids are available in many forms including solutions, tablets, capsules, syrups, injectable liquids, skin patches, and transmucosal forms, which all fall into one of two categories: short- or long-acting. Short-acting forms typically last between three and six hours, while long-acting forms last from 12 to 24 hours, reducing the frequency of consumption required to maintain their effect.[21] In addition, the illicitly manufactured opioids heroin and fentanyl are opioids that are currently present in Canada.

1.3 The opioid epidemic and the role of prescription opioids

Canada is facing an opioid crisis that has taken the lives of thousands of individuals and left many others living with opioid-related harms.[22] Between 2016 and 2021, over

22,000 apparent opioid-related deaths and over 26,000 opioid-related poisoning hospitalizations were reported nationwide.[23] Opioid poisonings resulted in over 16 hospitalizations per day in 2016 and 2017, of which one-half were considered accidental.[24] Between 2007-2008 and 2016-2017, opioid-related hospitalization rates increased by more than 53%. The greatest rate of growth was seen in youth (15-24 years) and young adults (25-44 years), although the highest overall rate of opioid-related hospitalizations was among older adults (45-64 years) and seniors 65 and older (20 per 100,000; age adjusted).[24] The COVID-19 pandemic exacerbated this crisis, with a reported 66% increase in opioid-related deaths and 20% increase in hospitalizations in the period from April to June 2021 compared to the same period from 2019.[23] Hospitalization costs due to opioid-related disorders alone were estimated at approximately $15 million in 2011 in Canada[25], but the amount attributed to prescription opioids only is not known.

The opioid crisis has been driven by the use of prescription opioids and illicitly manufactured heroin and fentanyl. The crisis initially began as a consequence of widespread opioid prescribing and was therefore dominated by harms related to prescription opioid use.[26] Currently, the largest burden in the epidemic is posed by the use of fentanyl and fentanyl-analogues, particularly in relation to opioid-related deaths. Still, prescription opioids remain important contributors to the epidemic. Sproule et al. found that 37% of those treated for oxycodone-related opioid use disorder at the Centre for Addiction and Mental Health in Toronto, Ontario between 2000 and 2004 reported physician prescriptions as their sole source of opioids, while 21% reported supply from the street, and 26% from both sources.[27] Among all individuals who had an opioid-related death in Ontario between 2013 and 2016, about one-third had an active opioid

prescription on the date of death.[1] A recent preliminary report from the Ontario Drug Policy Research Network found that, prior to the COVID-19 pandemic, hydromorphone, oxycodone, morphine, and codeine directly contributed to mortality in 30.5% of those who had opioid-related deaths.[28] Furthermore, from January to March of 2021, 29% of opioid-related poisoning hospitalizations involved fentanyl or a fentanyl-analogue – the remainder involved non-fentanyl formulations. These findings highlight the role prescription opioids play in the current crisis facing Canada and how they contribute to the development of opioid-related harms such as opioid use disorder.

1.4 Opioid prescribing for acute pain in Canada

Prescription opioid use is prevalent in Canada. Prescription opioid dispensing decreased slightly nationwide since the implementation of comprehensive dispensing policies in 2012[29], but their use remains widespread. Two national surveys found 1 in 8 adults (over 3 million individuals) reported past-year use of prescription opioids in 2017 and 2018, making Canada the second largest per-capita consumer of opioids worldwide.[2,6,30]

Acute pain is a common indication for which opioids are prescribed. Acute pain can be categorized into surgical and non-surgical pain, including trauma, musculoskeletal, orofacial, and other types as presented in Table 1.[31] The effective relief of acute pain is needed to avoid undue suffering and promote optimal healing.[31,32] Presentations for acute pain occur in a variety of settings including, but not limited to, the primary care setting, surgical care setting, emergency care setting , and dental care setting. Primary care doctors represent a large group of prescribers of opioids to patients with both chronic and acute pain in Canada.[33]

Each year, thousands of surgeries are performed in Canada, of which many are associated with postoperative pain requiring adequate pain relief. From April 2016 to March 2017, 177,293 surgeries in Canada involved the hip, knee, or fractured bones. [34] Overall, hip replacement surgery, knee replacement surgery, and surgeries for fractures were the second, third, and fourth highest volume inpatient surgeries performed nationwide in the year from April 2016 to March 2017, only exceeded by caesarian section deliveries.[34] These surgeries are associated with significant pain in the postoperative period.[35] A comparison between multiple developed countries showed that among those who had various low-risk surgical procedures between 2013 and 2016 in Canada, 78.6% filled opioid prescriptions within seven days of discharge.[3]

Painful conditions related to injury and trauma are also common reasons for presentation to the emergency department and hospitalizations: 269,694 individuals were hospitalized for injuries including falls, burns, and motor vehicle collisions in 2017-2018.[36] Over 10.6 million emergency department visits were reported in 2017-2018 to the National Ambulatory Care Reporting System (NACRS), representing 65% of emergency department facilities nationwide.[37] Abdominal, pelvic, chest, and back pain, and wounds to the hand and wrist were the most common conditions for presentation.[37] In a random sample of patients presenting with non-urgent low back pain to a large emergency department in Nova Scotia, opioids were prescribed to 38.5% of patients at discharge. [4]

Opioids are also commonly prescribed by dentists for oral pain and dental procedures. Approximately 12% of respondents to the 2007-2009 Canadian Health Measures Survey reported oral pain in the previous year.[38] In any two-year period, about 86% of Canadians visit a dentist.[39] Between 2011 and 2015, 75.6% of licensed dentists in Nova Scotia,

representing 17% of all opioid prescribers[5], wrote an opioid prescription that was filled by an adult patient.

1.5 Opioid-naive populations as a subgroup of interest

Opioid-naive populations are of particular interest in studying the safety of opioid prescribing for acute pain. In 2018, 8.1% of the Canadian population started opioids while opioid-naive.[6] To be opioid naive is to not be opioid tolerant. Tolerance is the diminishing effect of a drug after being exposed to it repeatedly or for a prolonged period, or the need for higher doses to maintain the same effect over time.[40] Therefore, patients who are opioid tolerant have different opioid requirements to achieve the same analgesic effect from those who are naive. For those with acute pain who are opioid naive, using opioids briefly and discontinuing use promptly after the pain has subsided can provide the benefits of pain relief without exposure to the risks associated with prolonged use, an advantage that they retain over those with previous repeated or prolonged opioid use.

From a clinical standpoint, a patient using opioids repeatedly or on a daily basis is considered to likely be 'opioid tolerant'. As such, researchers frequently define opioid naivety as no recent documented use of opioids at the time of presentation to the healthcare system. Further discussion related to measuring opioid naivety is presented in section 1.8.5 of this Chapter.

Many patients who start using opioids for acute pain conditions are opioid naive at the time. In 2016 alone, of 1.3 million opioid-naive individuals who started using opioids in Ontario, two in five received their prescription from a surgeon or dentist, likely to

manage acute pain.[33] Over a four-year period from 2014 to 2018, more than 780,000 opioid-naive individuals in Ontario filled opioid prescriptions issued by a dentist.[41]

1.6 Prolonged opioid use

1.6.1 Definition of prolonged opioid use

Prolonged opioid use generally refers to use beyond what was prescribed by the healthcare provider to treat acute pain for a short period.[42] Acute pain usually resolves within seven days, and does not frequently extend beyond one month.[31] However, a growing number of studies have shown that a proportion of those who were previously opioid-naive but started using opioids to treat acute pain did not discontinue use within the expected short-term time period; rather, documented prescription fills were seen beyond three months from the acute pain event.[10,12,43] In this context, long-term opioid use is frequently referred to as prolonged opioid use, which is thought to be unintended when the prescription was originally issued.[42]

1.6.2 Outcomes of prolonged opioid use

While initiating short-term use of opioids to manage moderate to severe acute pain related to injury, surgery, and other acute pain conditions in acute care settings is considered a cornerstone of pain management in North America, initiating opioids for long-term use should generally occur outside of the acute care setting. Initiation of opioids for prolonged use requires following stricter criteria for patient selection, sufficient planning for long-term follow up and monitoring, and establishing treatment agreements compared to only short-term use.[44,45] Currently, the Canadian opioid prescribing guideline for chronic non-cancer pain recommends that physicians prioritize non-opioid therapies for the treatment of chronic pain.[45] When opioids are being

considered, patients should be screened for relevant co-morbidities and dosing should be monitored carefully.[45] The United States (US) Centres for Disease Control (CDC) guideline further recommends that when physicians in primary care initiate opioids for chronic pain, treatment goals are established at the start, and that monitoring for benefits and harms is carried out regularly.[44] Acute care provision, unlike chronic or long-term care, ends once the acute event has resolved and is therefore unlikely to be the setting in which long-term monitoring may occur.

For some patients, long-term opioid therapy is deemed appropriate for the treatment of chronic pain. In Canada, 17.6% of all individuals who were prescribed opioids in 2018 were using them long-term (i.e., 90 or more days) – 24.8% in those 65 years or older, but <0.7% in those younger than 25 years.[6] Despite its use in this context, there is limited evidence about the effectiveness of opioid use for chronic pain management. Until a few years ago, little was known about the effectiveness of opioid therapy for pain relief and function in the long term despite widespread use.[7] A systematic review of randomized clinical trials that used indirect comparisons between opioids and alternative therapies concluded that none of the compared therapies, including opioids, provided clinically important pain relief improvements for patients with chronic pain compared to placebo.[46] Another systematic review of randomized clinical trials published in 2018 found that compared to placebo, opioids provided small benefits for pain relief and function that did not reach clinical importance, no differences were found when compared to alternative therapies including non-steroidal anti-inflammatory drugs, anticonvulsants, tricyclic antidepressants, and synthetic cannabinoids.[47] A randomized clinical trial comparing 12-month pain and function outcomes between opioid vs non-opioid therapies in patients

with chronic back pain or hip or knee osteoarthritis pain found that pain-related function did not differ between the compared groups, and pain intensity was lower among the non-opioid group.[48]

Prolonged opioid use is associated with an increased risk of opioid-related harms and other adverse outcomes. A systematic review by Chou et al. [7] on harms associated with the use of opioids for chronic pain reported that, compared to those using non-opioid therapy, patients using opioids for longer than 90 days over a 12-month period were 14.9 times more likely to experience opioid abuse or dependence.[7,13] Long-term opioid users were found to have 1.3 times the risk for any fractures[7,49] and 2.7 times the risk for myocardial infarction compared to non-opioid users.[7,50] Opioids are generally found to have a worse adverse events profile compared to placebo[46,51] and other alternative drugs [48] [47] in randomized clinical trials.

Prolonged opioid use may also be associated with higher healthcare costs compared to short-term use, as reported in multiple, large population-level US studies. [52-55] In a cohort study of over 250,000 patients, the healthcare utilization costs of opioid-naive non-cancer patients who used opioids for over six months more than doubled compared to before opioid initiation. [52] Compared to only brief use, prolonged opioid use was associated with greater inpatient healthcare use and expenditures after adjusting for many important covariates. [53] Opioid-naive patients who continued to use opioids throughout the year following an index prescription were seven times as likely to be hospitalized with opioid-related harms compared to those who only used them briefly.[54] Furthermore, compared to opioid-naive patients, those who used opioids in the preoperative period were found to have longer average hospital stays, higher 30-day re-admission rates, and

overall higher healthcare expenditures at 90, 180, and 365 days following surgery after adjusting for important confounders.[55] While the previous findings add an additional lens to understanding the impact of long-term opioid therapy on communities and healthcare systems, adequacy of adjustment for important covariates is not fully understood; therefore, findings must be interpreted with caution.

1.6.3 Risk of prolonged opioid use following new use for acute pain among opioid-naive populations

A small risk of prolonged opioid use following new use for acute pain related to surgery or injury and trauma was consistently reported in previous studies. Evidence presented in five systematic reviews found that among opioid naive subjects who received opioid prescriptions for surgery or trauma, between 1.2% and 10.4% were still using opioids at three to six months[8-12], with the majority finding the risk to be around 4% at six months.[8-10] Another review assessed risk of prolonged use after treatment with opioids for acute musculoskeletal injuries and found that risk was between 6% and 27%, depending on the risk category.[43] In summary, across systematic reviews, the reported risk of prolonged use after surgical care and care for injury or trauma among previously opioid-naive individuals substantially varied at 3 to 6 months.

1.6.4 Risk factors for prolonged opioid use

A number of patient characteristics and prescription factors were previously investigated as potential risk factors for prolonged opioid use. However, studies show inconsistency in whether, or how strongly, these factors are associated with the risk of prolonged opioid use.[54,56-68] Investigated patient factors included sex, age, history of psychiatric illnesses, history of substance abuse, and the presence of comorbidity;

findings about association with risk of prolonged use varied across studies.[57,58,60,61,65-68] A systemic review of studies of patients with chronic non-cancer pain found up to 76 different factors were assessed across studies to identify important risk factors for transitioning from short- to long-term opioid use.[69] The factors most frequently found to have an important association with transitioning to long-term opioid use in previously opioid-naive populations were tobacco use, drug use disorders, mental health disorders, arthritis, and chronic pain.[69] Whether similar results would be observed in patients with acute pain is not clear.

Another set of factors that were investigated for their potentially important role in risk of prolonged opioid use are first-prescription factors. Findings about the association between longer days' supply and prolonged opioid use across studies are inconsistent. Some studies found that first prescriptions that are longer in days' supply are associated with a higher risk of prolonged use,[41,62,70,71] but other studies did not.[72,73] Similarly, some studies found a weak overall association between higher first-prescription dose and prolonged use,[41,62,70,71] one found a moderate association,[70] but others found no association.[72,74] Inadequate adjustment for important confounders due to data availability,[41,70] using statistically-driven approaches to confounder selection,[72,74] and analysis of dose using categorization instead of continuous measures[41,62,70-72] have all contributed to the inconsistency of estimated associations observed across studies.

1.7 Prescribing patterns and determinants of variation in prescribing

1.7.1 Clinical practice guideline recommendations

Clinical guidelines for opioid prescribing for acute pain are currently limited. The most influential guidelines around opioid prescribing for acute pain have been the US CDC guidelines that were published in 2016 which advise physicians to start with short-acting opioids in the lowest effective dose for three days on average and no more than seven days, except on rare occasions.[44] The guideline however focuses on acute pain management in primary care and excludes those with postoperative pain. Canada does not have national opioid prescribing guidelines for acute pain related to injury or surgery or for the emergency and surgical care settings, as all healthcare policies are managed and administered on a provincial level. Ontario, British Columbia, and Nova Scotia have formal guidelines, but none are setting specific. In Ontario, clinicians are advised to prescribe short-acting opioids in the lowest effective dose for acute pain, and to prescribe them for three days or less, and seven days are rarely indicated.[75] Similarly, guidelines from 2016 in British Columbia instruct physicians to prescribe short-acting opioids for three to seven days when treating acute pain.[76] Furthermore, in Nova Scotia, 2020 the *Professional Standards Regarding Initiation of Opioid Therapy for Acute Pain* indicate that when opioids are initiated, short-acting opioids should be prescribed in the lowest effective dose and supply should not exceed seven days except if *extenuating circumstances* are documented clearly or reassessment of the patient has occurred.[77]

The Washington Agency Medical Directors' Group (AMDG) and Bree Collaborative 2018 guidelines addressing prescribing opioids for postoperative pain recommended

stratifying postoperative pain by expected recovery duration and prescribing short-acting opioids for ≤3 days with rapid recovery, ≤7 days with medium-term recovery, and ≤14 days with longer-term recovery. [78] The American Clinical Practice Guidelines for Pain Management in Musculoskeletal injury recommend prescribing short-acting opioids for the shortest period possible in the lowest effective dose.[79] A summary of a select group of existing guidelines is presented in Table 1-2. The guidelines were not identified following a comprehensive search; rather, the mostly widely used guidelines and local Canadian guidelines were included for consideration.

1.7.2 Prescribing patterns and physician factors as potential determinants of variation

Not all opioid prescriptions in excess of guideline thresholds should be immediately interpreted as inappropriate. Guideline recommendations are meant to guide care for most patients and to be adhered to when possible and appropriate; variations in patients' needs create exceptions. Patients with severe acute pain in need of effective pain relief that promotes healing and encourages early mobilization may require prescriptions that are written in higher doses and longer durations than the average patient presenting with acute pain. However, there are two problems that have been identified in opioid prescribing for opioid naive patients with acute pain that suggest that variation in prescribing may not always be explained by differences in patient needs.

The first problem is over-prescribing, as evidence shows that physicians frequently prescribe opioids in excess of patient need. A Canadian study on adults who were discharged from the emergency department with an opioid prescription found that, on average, patients consumed less than one-third of their opioid supply.[15] Similarly, a

systematic review of the quantity of opioids consumed after surgery found that between 42% and 71% of quantity filled was not consumed.[14] The second problem identified is the observed variation in opioid prescribing that is explained by prescriber factors rather than patient characteristics and their clinical need. Researchers found that independent of patient characteristics, opioid prescribing patterns varied by prescriber factors such as specialty[17], rank[18,19], and time constraints during provision of care.[20] A survey of 500 physicians who treat postoperative pain found the motivation for the choice of pain medication administered immediately after surgery was primarily based on past clinical experiences (81.6%), even more so than surgery type (78.2%). Only 41.9% of physicians cited adherence to clinical practice guidelines or protocol recommendations, and 35.1% cited review of the medical literature.[80] These research findings collectively suggest that prescribing conventions and shared clinical experiences among physician groups may influence prescribing decisions in the surgical and emergency care settings, independent of patient need.

1.8 Gaps in existing evidence and opportunities for this thesis

1.8.1 Risk of prolonged use

The existing synthesized evidence on risk of prolonged opioid use following new use for acute pain related to surgery or injury, or in the acute surgical and emergency care setting more broadly, is limited due to a lack of quantitative analysis (i.e., only narrative analysis was provided), [1012] no assessment of overall certainty in evidence, [101211] or because reviews did not focus on opioid-naive subjects[9]; the risk of prolonged use after acute pain in previously non-naive subjects is found to be between 5- and 12-fold higher than in those who are opioid-naive.[10,12] The review that did conduct quantitative analysis

and assessed overall certainty in existing evidence had a narrow population[43], and whether results would apply for other acute pain groups for which opioids are commonly prescribed, namely surgical and dental patients, is unclear. Furthermore, at the time of thesis proposal development, no systematic reviews had synthesized evidence on prolonged opioid use following new use for dental-related pain, leaving gaps in knowledge for this group of patients.

Quantitative analysis and assessment of overall certainty in existing evidence will add valuable evidence to the literature used to guide decision making in this area. Reliable synthesized estimates of overall risk of prolonged use can help shed light on the scope of the problem across all jurisdictions in which opioids are frequently prescribed for opioid-naive patients with acute pain.

Furthermore, there are currently no studies that investigated risk of prolonged use in Nova Scotia. Estimating risk locally will allow decision makers to determine how prevalent the problem is and how it compares to the global average. With widespread prescribing, even a small proportion of patients becoming long-term users after acute pain management amounts to a large absolute number of long-term opioid users added to the community each year.

1.8.2 Important patient characteristics

To identify important patient risk factors for prolonged use in previously opioid-naive populations treated for acute pain, a synthesis of existing evidence is needed.

Applicability of existing reviews that summarized evidence about patient characteristics and risk of prolonged use in patients being treated for acute pain is limited because in their analysis of risk factors, they did not limit studies to those that included

opioid-naive individuals.[9-12] Evidence has consistently shown that individuals receiving opioids for acute pain who have pre-existing opioid use show markedly higher rates of prolonged use compared to opioid-naive individuals.[9,10,12] Thus, restricting study populations to opioid-naive individuals eliminates the potential confounding effect of pre-existing opioid use and allows for better estimation of the association between other risk factors and prolonged use. A review on prolonged use after treatment for musculoskeletal injury[43] which did include an opioid-naive population included a restricted acute pain population and whether results would be generalizable to other settings and acute pain populations is not clear.

A synthesis of the evidence needs to consider the potential risk of bias in included studies and must assess overall certainty in the available evidence to support further research and guideline development. Important risk factors shed light on at-risk populations for whom prescribing opioids with more caution may be warranted. Identifying important risk factors can also support researchers in developing risk prediction models or clinical decision-making tools that are of value to clinicians treating opioid-naive patients presenting with acute pain who want to identify individuals at high risk for prolonged opioid use. [81] All existing tools today were developed for patients with chronic pain for whom a chronic opioid use regimen is being considered.[82,83]

1.9 Association between first-prescription factors and risk of prolonged use

The prescribing needs of opioid-naive populations differ from those on long-term opioid therapy. The outcomes associated with prescribing patterns may also differ in important ways, affecting what constitutes safe prescribing. More evidence on important

first-prescription factors that may be associated with higher risk of prolonged opioid use is needed due to the scarcity in existing evidence in this area and its limitations. While prolonged use is only one of several outcomes that need to be considered for safe prescribing, providing reliable evidence for the risk of prolonged opioid use that is associated with various prescribing patterns will nonetheless provide valuable information for guideline development and clinical decision making and will also contribute to better benefit-harm balance, which has been identified as a priority for acute pain management with opioids.[84]

Furthermore, a potentially important consideration for understanding the association between dose and prolonged use is whether an interaction between dose and days' supply might exist. However, this has not been explored in previous studies. There is evidence that various combinations of dose and length of treatment affect risk of developing opioid use disorder differently in patients with chronic non-cancer pain[13], suggesting that exploring a similar pattern in opioid-naive populations being treated for acute pain may provide important insights.

1.9.1 Prevalence of prescribing in high-dose, long duration, or for long-acting formulations, and association with setting and provider specialty

Currently, little is known about opioid prescribing patterns in opioid-naive populations presenting with acute pain in Canada more broadly and Nova Scotia more specifically. Some studies described patterns of prescribing, but included populations with pain regardless of pain acuity,[33,71] or restricted study populations to a single setting.[70] Monitoring of prescriptions longer than 7 days' supply or high in dose has been

recommended for opioid-naive populations presenting with acute pain.[75] Estimating the prevalence of prescribing in excess of one week or in high-dose or long-acting formulations will contribute to our understanding about the safety of prescribing opioids to opioid-naive populations in acute care settings, and may inform us about their unique needs. Setting and provider specialty can serve as proxies for common clinical and training experiences among physician groups and exploring whether prescribing differs across those categories may shed light on potential influencers of certain prescribing patterns.

1.9.2 Methodological considerations for measuring opioid naivety and prolonged opioid use

Opioid naivety and prolonged opioid use are two constructs that are not well defined clinically, and researchers have not reached consensus about how they should be measured. Below I highlight conceptual and methodological considerations for measuring the constructs in the current thesis.

Opioid naivety status is frequently measured using prescription opioid filling in research studies. Definitions of naivety vary with respect to the required duration of no use. Some researchers consider patients to be opioid-naive if they had no documented opioid prescriptions filled during the three[66] or six[60,63,70,85] months preceding presentation for care, while others require a minimum of one[54,58,59,64,65,86] or two[41] years of no use. Some researchers exempted use in the 30 days prior to surgery to account for preoperative prescribing conventions in study settings. [57,61]

Because opioid metabolism varies among people and markers of metabolism are not readily used in clinical practice[87], the more accurate a definition is in capturing non-daily use (i.e., likely non-tolerance), the more reliable the definition may be for use in

measuring naivety. Daily use can occur in patients who have not filled opioids in the past 30 days if they have prescriptions with a supply that exceeds that period. Similarly, a patient who uses opioids daily and has a prescription that is longer than 90 days may be misclassified as opioid naive when the definition relies on a 90-day period. Some physicians prescribe opioids for up to 90 days to patients with chronic pain on long-term opioid therapy. On the other hand, there is likely a small chance that a patient who uses opioids daily or on a regular basis would have a prescription with a days' supply of over six months. A definition of no documented opioid filling for six months (i.e., 180 days) is therefore less likely to misclassify regular or recent opioid users as opioid naive.

There are also some issues in measuring prolonged opioid use that need to be considered. There is wide variation in how the construct prolonged opioid use has been defined across studies, with researchers having set minimum thresholds for duration and quantity of use at various points (Appendix 1-A). In research that included opioid-naive populations treated for acute pain, terms used in addition to prolonged use included recurrent use, new persistent use, long-term use, chronic use, and failure to discontinue use [56-58,61,65] All of these definitions were intended to be used to identify patients who continued to use opioids beyond the expected short-term period for acute pain. With the expectation that acute pain will not exceed 30 days[31], and evidence showing that prolonged opioid use (defined as use for ≥90 days)[69] is associated with higher risks of harm to individuals[7], a definition of prolonged opioid use measuring use beyond 90 days can be considered clinically meaningful and relevant to studying outcomes of opioid prescribing for acute pain.

Measures reflecting continuous use during the follow-up period minimize the possibility that opioid discontinuation followed by new opioid prescription filling for new, unrelated events is misclassified as prolonged use. One such measure required that a subject fills at least one opioid prescription in the preliminary period from the acute pain event to three months, in addition to filling a prescription during the relevant time period beyond three months.[70] Another measure required a supply to cover most days during the follow-up period[63], and a third definition measured time to discontinuation of use as opposed to measuring additional use.[62] A fourth approach to increase the likelihood of measuring continuous use was excluding – either in the main study or in a sensitivity analysis – those with events that may require additional opioids to be prescribed during follow-up, such as additional procedures.[57]

In summary, measures of prolonged use that depend on objective measures of prescription filling and capture use beyond 90 days from the main acute pain event or first prescription, in addition to incorporating some measure of continuous use to 90 days, seem to address all of the conceptually important elements of prolonged use in the context of continuous use after new prescribing for acute pain.

1.9.3 Conceptual framework for prolonged opioid use

I created a conceptual framework that depicts the transition of patients with acute pain from being opioid naive to becoming prolonged opioid users. Risk of opioid related harms is lowest when the patient remains opioid naive, increases as they start using opioids, and continues to increase as their use persists. As the focus of this thesis is on opioid naive patients newly starting opioids, I focus on the transition from short-term use to prolonged use, and I include potential risk factors drawing from Hooten's conceptual

framework and available evidence. In addition to the patient, prescriber, and practice-environment factors included in the Hooten framework, I include prescription factors including opioid dose, days' supply, and type (Figure 1-1).

1.10 Thesis Aims and Objectives

Overall aim: The overall aim of this thesis is to contribute to the available evidence base on prolonged opioid use following new opioid use for acute pain, as well as the prescribing patterns for opioid-naive patients with acute pain or presenting to surgical and emergency acute care settings, and to inform future research in this area.

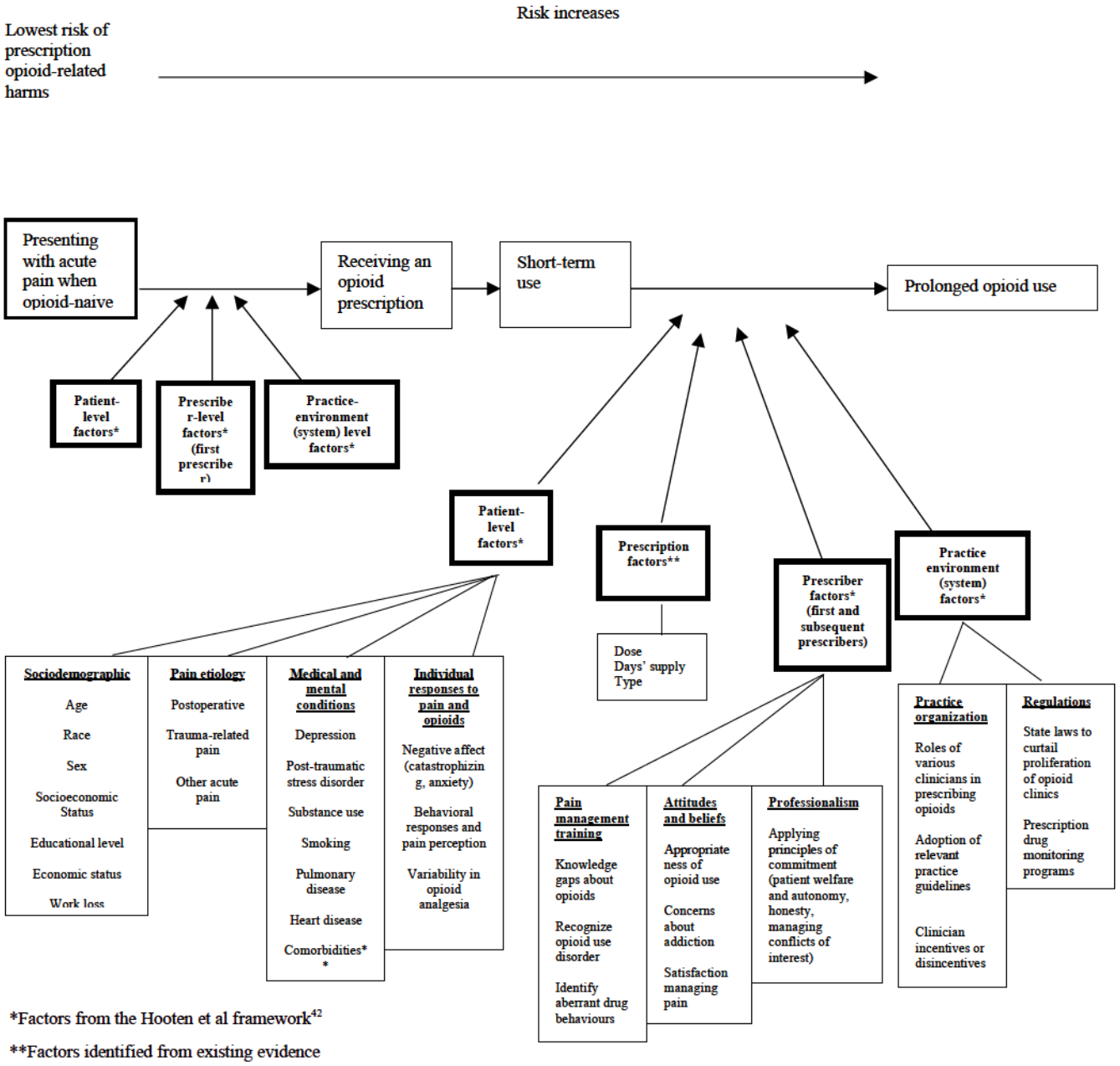
Evidence synthesis (Objective 1): The first objective was to identify, assess, and summarize the existing evidence on the overall risk of prolonged opioid use following new opioid use for acute pain in opioid-naive populations, and to synthesize the existing evidence on the association between baseline patient demographic and clinical characteristics, first-prescription factors, and prolonged opioid use. This objective was addressed in the first study included in the current thesis.

Prescribing patterns (Objective 2): The second objective was to: (1) describe the characteristics of all opioid prescriptions that were filled by opioid-naive adults in community pharmacies within 14 days of surgical or emergency care; (2) determine the prevalence of filled prescriptions that exceeded 7 days, 90 morphine milligram equivalents (MME)/day, or were for long-acting opioids, strong opioids, or tramadol; and (3) determine whether setting and provider specialty were associated with these outcomes, adjusting for patient characteristics. The second study included in this thesis addresses this objective and was guided by the following research questions: (1) What is

the average daily dose in MME and average days' supply of the prescriptions filled? (2) What was the distribution of filled formulation types? (3) What proportion of filled prescriptions exceeded 90 MME/day, 7 days' supply, or were for a long-acting opioid? (4) Does prescribing in excess of 90MME/day, 7 days' supply, and long-acting opioids differ across settings and specialty in general, and after adjusting for patient characteristics?

Prolonged opioid use (Objective 3): The third objective included in this thesis was to: (1) estimate the risk of prolonged opioid use after filling an opioid prescription following surgical and emergency care in opioid-naive adults in Nova Scotia; (2) assess the association between average daily dose, days' supply, and opioid type (long- versus short-acting) of the first filled prescription and prolonged use, after adjusting for important co-variates; and (3) determine whether the association between dose and prolonged use differs by days' supply. The guiding research questions for this study were: (1) What is the risk of prolonged opioid use for opioid-naive adult patients who fill opioid prescriptions following surgical or emergency care in Nova Scotia? (2) Are first prescriptions with higher doses and longer days' supply and those for long-acting opioids associated with a higher risk of prolonged opioid use in this population after adjusting for important patient and prescription co-variates? (3) Does the association between dose and prolonged use differ by prescription length (i.e., days' supply)?

Figure 1-1: Prolonged opioid use conceptual framework



*Factors from the Hooten et al framework[42]

**Factors identified from existing evidence

Tables

Table 1-1: Acute Pain Categories (Modified from Table 5 in The ACTTION–APS–AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions.)[31]

Acute Pain Categories	
Surgical/Procedural	**Nonsurgical**
General surgery	Trauma (including burns)
Orthopedic surgery	Orofacial
Obstetric/gynecologic surgery	Musculoskeletal
Plastic and reconstructive surgery	Acute neuropathic (e.g., radiculopathy)
Otolaryngology	Acute ischemic (e.g., myocardial ischemia)
Urology	Visceral (e.g., renal colic)
Cardiovascular surgery	Special populations
Thoracic surgery	Adolescent
Transplant surgery	Cancer
Neurosurgery	Elderly
Dental surgery	Labour
Ophthalmic surgery	Pediatric/neonatal/fetal
Out of operating room procedures	Sickle Cell
Pediatric surgery	Other

Table 1-2: Examples of opioid prescribing guidelines in Canada and the United States – focus on recommended dose, duration, and type.

Guideline	Year	Country	Type of pain	Recommendations focused on opioid-naive?	Stratification by other patient characteristics?	Dose recommendations	Days' supply recommendations	Type of opioid recommendations
The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain[45]	National panel	2017 Canada - national	Chronic non-cancer	Yes - Stratified by opioid use status to initiating or on long-term therapy	Yes – history of past or active psychiatric disorder and/or substance use disorder	For those initiating long-term opioid therapy: restrict to <90MME/day (strong rec); restrict to <50MME/day (weak rec)	NA	For those initiating long-term opioid therapy: Expert opinion only given – inconclusive evidence
CDC Guideline for Prescribing Opioids for Chronic Pain – United States[44]	Centers for Disease Control and Prevention, Atlanta, Georgia.	2016 US - national	Chronic non-cancer in primary care, with limited guidance for acute pain in primary care	No	No – but individual risk to be assessed	Acute pain: lowest effective dose Chronic pain: reassess evidence of benefit with ≥50MME/day; avoid or carefully justify ≥90MME/day	Acute pain: Base on expected duration of pain: ≤3 days frequently sufficient. >7 days rarely needed.	Acute pain: Short-acting
Prescribing Opioids for Postoperative Pain – Supplemental Guidance[78]	The Washington State Agency Medical Directors' Group (AMDG) and the Bree Collaborative	2018 US – state-level	Acute -postoperative	Yes - Separate section for those on chronic opioid therapy.	No – individual risk to be assessed	Lowest effective dose	Expected recovery duration/type of procedure: rapid ≤ 3 days; medium-term ≤ 7 days; long-term ≤ 14 days. Do not exceed 14 days for any initial prescriptions.	Short-acting
The American Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury[79]	Orthopedic Trauma Association Musculoskeletal Pain Task Force	2018 US - national	Acute – musculoskeletal injury	Yes - Separate section for those on long-term opioids.	Yes – type of injury and procedure	Lowest effective dose	Shortest period depending on severity of injury/procedure	Short-acting. Do not use extended release opioids.
Quality Standards for Opioid Prescribing for Acute Pain	Health Quality Ontario	2018 Canada – provincial	Acute – all care settings	Yes	Comprehensive assessment needed	For clinicians: lowest effective dose Quality indicator: Monitor proportion of prescriptions that are >50 MME/day	For clinicians: ≤ 3 days often sufficient; > 7 days rarely indicated Quality indicator: Monitor proportion of prescriptions that are ≤ 3 days; > 7 days	For clinicians: short-acting Quality indicator: proportion of prescriptions for long-acting opioids
Management of post-operative pain: a clinical practice guideline	American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia	2016 US - national	Acute post-operative; focused on the immediate post-operative period, not post-discharge	NA	NA	NA	NA	NA
Professional Standards and Guidelines: Safe Prescribing of Drugs with Potential for Misuse/Diversion	College of Physicians and Surgeons of British Columbia	2016 Canada - provincial	Acute and chronic - Focused on prescribing of drugs with potential for misuse/diversion	No	Individual risk of psychiatric illness and substance use disorder to be assessed when initiating opioids for long-term use	Lowest effective dose. For long-term therapy: reassess with ≥50MME/day; avoid ≥90MME/day	Only quantity that patient will need before community follow-up (3 to 7 days usually appropriate)	For acute pain: Short- acting

Professional Standards Regarding Initiation of Opioid Therapy for Acute Pain	College of Physicians and Surgeons of Nova Scotia	2020	Canada	Acute pain in the outpatient setting	Not clearly stated, but likely given focus is on opioid *initiation*	Assessment for risk of opioid misuse including history of substance use, psychiatric illness	Lowest effective	Three days sufficient; more than seven days needs to be justified and clinically documented

Appendix 1-A Examples of prolonged opioid use definitions used in previous studies.

Prolonged use definition	Minimum quantity of prescription fills required	Time period from acute pain episode (days)	Study
Prolonged opioid use defined as opioid use at 12 months post-surgery	Continuous filling defined as filling with <14 days' supply gap	12 months (~365 days)	Hadlandsmyth et al. (2018)[67]
Continued/sustained opioid use defined as a consistently filled prescription for one or more opioid medications, beginning within 30 days of discharge and continuing with no more than 30 days elapsing between prescription refills.	Continued use defined as no more than 30 days elapsing between fills	90 days, 180 days	Schoenfeld et al. (2017)[63]
Rates of use at each month following surgery was reported.	One	Each month (~30 days) up to 12 months (~365 days)	Westermann et al. (2017)[68]
Long-term opioid use defined as 180 days or more of opioids supplied in the 12 months after an index emergency department visit, excluding prescriptions within 30 days after the index visit.	180 days' supply	31 days to 12 months (~365 days)	Barnett et al. (2017)[85]
Probability of continued use at 1 year and 3 years.	Continuous filling	One year (~365 days) and three years (~1,095 days)	Shah et al. (2017) (CDC)[56]
Probability of continued use at 1 year -- patients who continued opioid use for ≥12 months were those who did not meet the definition of opioid discontinuation within 12 months after the first opioid prescription. Opioid discontinuation defined as at least 180 continuous days without opioid use from end date of the last opioid prescription.	Continuous filling	12 months (~365 days)	Shah et al. (2017)[56]
New persistent opioid use defined as ≥1 opioid prescription fulfillment 90 to 180 days after surgery.	One	90 to 180 days	Brummett et al. (2017)[57]; Johnson et al. (2016)[61]

Long-term use defined as six or more opioid fills during the subsequent year following opioid initiation month (i.e. beginning after the first month).	Six	One month to one year (~31 to 365 days)	Deyo et al. (2016)[54]
Chronic opioid use defined as having filled 10 or more prescriptions or more than 120 days' supply of an opioid in the first year after surgery, excluding the first 90 postoperative days.	Ten OR 120 days' supply	91 days to one year (~365 days)	Sun et al. (2016)[65]
Chronic prescribing defined as prescribing lasting longer than 90 days and 120 or more total supply, or 10 or more prescriptions over one year.	Ten	One year (~365 days)	Hooten et al. (2015)[60]; Calcaterra et al. (2015)[64]
	120 days' supply	90 days	
Having medical bills for three or more prescriptions filled between 4 days and 12 months post-onset of injury, excluding any opioid prescriptions received during the initial emergency department visit.	Three	4 days to 12 months (~4 to 365 days)	Lee et al. (2016)[86]
Recurrent opioid use defined as filling any opioid prescription within 60 days of the first anniversary of index emergency department visit/surgery (i.e., 305 to 425 days after visit/surgery).	One	305 to 425 days	Hoppe et al. (2015)[58]; Alam et al. (2012)[59]
One or more opioid prescriptions within 1 to 90 days after surgery along with one or more prescriptions for opioids within 91 to 180 days after surgery.	One	91 to 180 days	Clarke et al. (2014)[66]
An uninterrupted opioid prescription for longer than 3 months after surgery.	"uninterrupted prescriptions"	Three months (~90 days)	Rozet et al. (2014)[88]
Chronic opioid use is defined as 10 or more opioid dispensations over 90 or more days or dispensations of at least 120 days' supply of opioids during the year after surgery.	Ten	90 days	Raebel et al. (2013)[89]
	120 days' supply	One year (~365 days)	
Continued taking new opioids 150 days post-surgery.	One	150 days	Carroll et al. (2012)[90]
Five or more opioid prescriptions between 30 and 730 days post-onset	Five	30 to 730 days	Webster et al. (2007)[91]

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2 Chapter Two: Overall risk and risk factors for prolonged opioid use following new use for acute pain in opioid-naive adults: A systematic review and meta-analysis of the evidence

2.1 Note to reader

In this chapter, I estimate the risk of prolonged opioid use following new use for acute pain or after receiving care in the acute care setting among opioid-naive adult populations. I also identify patient characteristics and first-prescription factors that are associated with a higher risk of prolonged opioid use. I used systematic review and meta-analysis methodologies to summarize the existing evidence, and used modified GRADE methodologies to assess certainty in the existing evidence.

2.2 Manuscript Information

Authors: Roah Merdad, Mark Asbridge, Samuel Campbell, Daniel J. Dutton, Jill A. Hayden

Status: A version of the manuscript will be submitted to *PAIN*. Second risk of bias assessment and re-running the search are required prior to proceeding with submission.

Permission: NA

Student contribution to the manuscript: Roah Merdad conceived the research question and designed the study along with her main supervisor, Dr. Jill Hayden. Roah developed the search strategy in consultation with a medical librarian, ran the search, screened titles and abstracts and full text citations using a screening tool that she developed for the study, extracted data using a spreadsheet that she developed for the study, conducted risk

of bias assessment, analyzed the data, conducted assessment of overall certainty of the evidence, interpreted results, wrote the first draft of the manuscript, and revised all subsequent drafts after input from coauthors.

2.3 Manuscript

2.3.1 Abstract

Background: We need to better understand what proportion of opioid-naive patients who have started prescription opioids after presenting to hospital with acute pain go on to experience prolonged opioid use, and to identify important risk factors linked to this outcome.

Objectives: To identify, assess, and summarize the existing evidence on the risk of prolonged opioid use following new use for acute pain in opioid-naive adults, and to synthesize the existing evidence on the association between baseline patient demographic and clinical characteristics, first-prescription factors, and prolonged opioid use.

Methods: We conducted a systematic review, and searched MEDLINE Ovid, EMBASE, PsycINFO, CINAHL, and Web of Science from inception to April 29th, 2019 to identify studies (cohort, case-control, or clinical trials) that have assessed the risk of and risk factors for prolonged opioid use in adult opioid-naive patients newly starting opioids for acute pain. We extracted data on study characteristics, population, risk factors, and the outcome; assessed risk of bias using criteria for event rates and a modified QUIPS tool for prognostic/risk factors; quantitatively synthesized data using random effects meta-analysis when possible. We assessed the overall certainty of evidence using modified GRADE criteria.

Results: We screened 1112 citations and included 35 studies (subjects: 2,037,051 surgery; 1,256,023 injury; 76,915 dental pain). We found moderate-certainty evidence that the risk of prolonged use is 6% following surgery (95% CI 4% to 9%; 2,037,051 subjects); 9% following injury (95% CI 6% to 12%; 1,256,023 subjects); and high-certainty it is 3% following dental pain (95% CI 2% to 6%; 76,915 subjects). We found high-certainty evidence that these factors are associated with higher risk of prolonged use: race (Black compared to white) (OR 1.24, 95% CI 1.19 to 1.29; 530,664 subjects); arthritis (OR 1.22, 95% CI 1.12 to 1.32; 1,265,215 subjects); anxiety (OR 1.22, 95% CI 1.15 to 1.30; 1,145,022 subjects); depression (OR 1.41, 95% CI 1.28 to 1.56; 1,763,427 subjects); and illicit drug use (OR 1.55, 95% CI 1.31 to 1.83; 1,562,034 subjects). We found moderate certainty evidence for the following factors: back pain (OR 1.25, 95% CI 1.14 to 1.36); neck pain (OR 1.12, 95% CI 1.06 to 1.17); alcohol use (OR 1.38, 95% CI 1.20 to 1.59); tobacco use (OR 1.47, 95% CI 1.24 to 1.75); and receiving tramadol or long-acting opioids (narrative synthesis: three studies, 1,272,760 subjects).

Conclusions: Prolonged opioid use is an important consequence of new opioid prescribing for opioid-naive patients with acute pain. Identified risk factors suggest that potential avenues for intervention may exist to allow more judicious prescribing and lowering risk of unintended prolonged opioid use. We suggest that based on our findings, more evidence is needed to reach a fuller understanding of the association between days' supply, average daily dose, and prolonged use in the studied population.

2.3.2 Introduction

The widespread use of prescription opioids has contributed to the current epidemic of opioid-related harms seen in Canada and the United States.[1,2] Compared to only short-term use or use of alternative pain relief medications, the risk of developing opioid-related harms including opioid use disorder and overdose substantially increases with opioid use for three months or longer. [3-7] A growing body of evidence has shed light on the possibility that opioid prescribing for acute pain to previously opioid-naive patients may be an important, frequently unintended, and potentially preventable segue to prolonged opioid use. While physicians may frequently prescribe opioids for opioid-naive populations following surgery, injury, or dental procedures with the intention of prompt discontinuation after the acute pain episode, over thirty recently published studies have shown that some of these patients will go on to become prolonged users.

There are currently no systematic reviews that quantitatively synthesized evidence about the risk and risk factors of prolonged opioid use in opioid-naive populations being treated for acute pain, or for pain presenting to the acute care setting more broadly. One recent review assessed risk and risk factors in patient presenting with musculoskeletal pain only.[8] Three reviews summarized evidence for opioid-naive subgroups – however, these reviews did not quantitatively analyze the evidence and did not assess overall certainty in it.[9-11] Another review assessed risk factors in opioid-naive and non-naive populations together[12]; previous opioid use is a strong risk factors for prolonged use[9,10] and its presence could introduce confounding when associations between patient and prescription factors and prolonged use are assessed. The variation in reported risks across these reviews – ranging from less than 2% to over 25% - inconsistent findings, and

general lack of assessment of certainty in evidence limits decision makers' ability to use the presented evidence to inform prescribing decisions.

A synthesis and overall assessment of certainty in existing evidence on the risk and risk factors of prolonged use in opioid-naive populations treated for acute pain, or in the acute care setting more broadly, is needed to help policymakers and physicians estimate the scope of the problem and identify important risk factors. This evidence can support physicians and guideline developers in stratifying patients according to risk level when patients are being considered for opioid treatment. Identifying modifiable risk factors like prescribing patterns can also inform decision makers and contribute to the evidence used to weigh harms and benefits of opioids prescribing for acute pain.

In this systematic review and meta-analysis, we aimed to identify, assess, and summarize the existing evidence on the risk of prolonged opioid use following new use for acute pain in opioid-naive adults, and to synthesize the existing evidence on the association between baseline patient demographic and clinical characteristics, first-prescription factors, and prolonged opioid use.

2.3.3 Methods

Study eligibility

Studies were eligible for inclusion if they were cohort or case-control in design or were clinical trials for which data on the arm randomized to opioids was presented. Studies must have included adults (18+ years), who were opioid-naive at the time of receiving a new opioid prescription for acute pain to be included. We defined opioid-naivety as no opioid use for a minimum of 30 days before the first prescription measured by self-reports, no documented fills in medical claims, or no documented prescriptions in

medical records. We also accepted definitions of no use for 11 months until 30 days preceding a surgical procedure. We defined acute pain as any pain type included in the ACTTION-APS-AAPM Pain Taxonomy or presenting to the emergency department. [13] Finally, to be included, studies must have reported a measure of prolonged opioid use as an outcome in the study. We accepted measures using fills in claims, prescriptions in medical records, and self-reports of use. We set the minimum timing of prolonged use to be at or beyond 60 days from the day of receiving or filling the first-prescription or acute pain diagnosis. For further details on selection criteria and decision thresholds for studies with mixed populations, see Appendix 2-A.

Search methods and study selection

We searched MEDLINE Ovid, EMBASE, PsycINFO, CINAHL, and Web of Science databases using search strategies that we developed in consultation with a medical librarian. We combined terms capturing: prescription opioids using all name variants; acute pain or the acute care setting including surgical, dental, and emergency settings; and prolonged opioid use using terms that included prolonged, long-term, longitudinal, persistent, chronic opioid use and failure to discontinue use. We searched all databases from inception and did not apply language filters. We present the full database search strategies in Appendix 2-B. We ran the search in all databases on the same day [April 29th, 2019]. We removed duplicate citations in EndNote X8 (Clarivate Analytics, PA, USA) and screened remaining citations using Covidence software (Veritas Health Innovation, Melbourne, Australia). We searched reference lists of included studies and identified reviews for additional relevant studies. We conducted title and abstract and then full text screening using a standardized tool (see Appendix 2-C). To date, two

review authors completed title and abstract screening, and one completed full text review. A second review author will independently screen full texts, and all disagreements will be resolved by consensus.

Data extraction and management

We used an Excel form to extract data on study characteristics, study population, risk factors, prolonged opioid use definition(s), and type of outcome analysis performed, whether it was adjusted, level of adjustment (suboptimal, sufficient, or ideal – details in Appendix 2-D) and the list of covariates. We extracted data on the risk of prolonged opioid use and on measured of association for risk factors (odds ratio, relative risk, hazard ratio, or beta coefficient) with 95% confidence intervals, standard errors, or exact p-values. We mapped each study population to one of the following acute pain groups: surgery; injury or ED-presenting pain; dental; or other (including acute pain not related to surgery, injury, or dental pain such as pain related to radiation-therapy and acute flare-ups of inflammatory medical conditions). We extracted any measure of prolonged use beyond 60 days and classified timepoints as: intermediate-term (60 days to 180 days), or long-term (more than 180 days).

Assessment of risk of bias in included studies

To assess risk of bias in estimates of risk, we followed guidance from Iorio et al. to assess study limitations that may underestimate or overestimate event rates. [14] We rated each included study in the following domains: study participation: the sample of patients in the study was well defined and representative of the target population; follow up and data completion: follow up was sufficiently long and complete; outcome

measurement: objective and unbiased measurement of prolonged opioid use was used (for details on judgement for this domain, see Appendix 2-D).

We also assessed risk of bias for each included study with respect to risk factors. We used a modified version of the QUality In Prognostic Studies (QUIPS) tool [15,16] and assessed risk of bias related to the following six domains: study participation, study attrition, risk factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. We rated study confounding based on adequacy of adjustment, with an ideal adjustment rating confounding as low, a minimum sufficient adjustment rating as moderate, and a suboptimal adjustment rating as high.

In studies that included multiple risk factors for which our assessment of risk of bias varied across factors, we used risk factor-specific assessment to inform the study limitations domain in the overall certainty of evidence assessment. However, for the overall risk of bias assessment for each study, the factor with the highest risk of bias was used in determining overall risk of bias. In both risk of bias assessments, we considered the overall risk of bias for a study to be low when we rated the risk of bias across all domains to be low, moderate when we rated one or more domains to be moderate without any domains being rated as high, and high when we rated one or more domains to be high.

Quantitative and narrative analysis

We estimated an overall risk of prolonged use with 95% confidence intervals for surgery, injury, and dental groups separately. We pooled data across studies and used a random effects meta-analysis when data was available from three or more studies in each group. For each included risk factor, we pooled data across all included studies

(regardless of acute pain group) and conducted random effects meta-analyses to estimate a measure of association with 95% CI when three or more studies used sufficiently similar measurement of the risk factor, and presented the same measure of association from any adjusted analysis [odds ratio (OR), relative risk (RR), or hazards ratio (HR)]. We narratively synthesized the evidence from studies presenting results of unadjusted analysis or those presenting HRs, RRs, and beta coefficients for which the minimum three-studies rule was not achieved. We determined whether each study estimate was associated with a lower, neutral, or higher risk of prolonged use and used a vote count.

Subgroup analyses

Subgroup analyses were conducted to determine risk by surgical subspecialty (seven groups), by whether surgery was performed in the injury pain group (two groups), and by timing of outcome measurement (intermediate term vs. long-term).

Sensitivity analyses

To assess the robustness of our findings about incidence, we conducted sensitivity analyses that included studies that measured continuous or frequent use in the follow-up period; studies that included only opioid-naive subjects; only studies that objectively measured opioid use at baseline in all included patients; and finally, only studies that were rated to be at low or moderate overall risk of bias. We also conducted sensitivity analyses for each risk factor to assess the potential impact of measurement properties, adjustment adequacy, and overall risk of bias. Stata version 14.2 was used to conduct all the analyses.

Assessing the overall certainty in the evidence

We followed adapted GRADE guidance provided by Iorio et al., Huguet et al., and Foroutan et al. and considered the total number of subjects, studies and cohorts, limitations across studies, inconsistency, indirectness, imprecision, publication bias, effect size, and the presence of a dose effect [14,17,18] to assess the overall certainty in the evidence. We considered in our assessment both the quantitatively and narratively synthesized evidence, to consider evidence in its entirety.

2.3.4 Results

Study identification and selection

We identified 1112 unique citations after applying the electronic search strategy and searching other sources (Figure 2-1). We screened 208 full-text citations and included 35 studies [19-53].

Characteristics of included studies

Thirty-five studies provided information about prolonged opioid use in opioid-naive patients newly starting opioids for acute pain and were included in the review. Of those, 25 studies with 26 cohorts included patients newly starting opioids for surgery (2,037,051 subjects)[19-23,25,28-35,37,39-43,45,48,49,51,53], 11 studies with 12 cohorts for injury (1,256,023 subjects)[19,20,24,27,34,37,38,44-46,51], four studies for dental pain (76,915 subjects)[26,46,51,52], and three studies for other types of acute pain[36,47,50]. All included studies were longitudinal cohort studies; the majority of which were retrospective in design (33/35), with only two prospective[24,28]. Fifteen of the included studies were published in 2019, 17 between 2016 and 2018, and only three before the year 2016. Most of the included studies were conducted in the United States (32/35), two in Sweden[19,20], and one in Australia[35].

Most included studies were population based (27/35) utilizing a range of data sources; national or state-wide public or private insurance claims databases[23,25,27,29,30,32,33,36-41,43,44,47-49,51-53], Veterans' health administrative databases[21,35], national or regional administrative databases including hospital discharge data, prescription drug monitoring data, and vital statistics data[19,20,26,47], or national survey data[46]. Eight studies were conducted in clinical settings, utilizing data from institutional administrative databases and research registries[22,34], electronic medical records or medical charts[42,45,47,50], or in which data was prospectively collected[24,28].

The sample size of included studies ranged from 109 subjects in a surgical clinical setting to 1,353,902 subjects across settings. Twenty-eight studies included study populations that were entirely (100%) opioid-naive at the time of newly starting opioids[19,20,23-27,29-35,37-39,43-53]. Nine of the included studies used multiple definitions, or measures, for prolonged opioid use[19-21,24,27,31,38,48,53]. Details about included studies are presented in Appendix 2-E.

Risk of bias in included studies

We rated the overall risk of bias in reported risks to be low in 23 studies[19-21,23-25,29-32,35-37,39-41,43,44,47-49,52,53], moderate in 9 studies[26,27,33,34,38,42,45,46,51], and high in 3 studies[22,28,50]. Assessment of risk of bias was low in many of the included studies across domains: study participation (27/35), follow up and attrition (26/35), and outcome measurement (27/35). We assessed risk of bias in estimates of association for the 29 studies that contributed data to risk factor analysis, with overall risk of bias moderate in 18 studies[21,23,25,27,29-34,39,40,42,43,47,48,51,53] and high in 11 studies[19,20,22,26,28,46,49] (Table 2-1). The main domains of concern were risk factor measurement (moderate 20, high 0) due to

the predominant use of diagnostic codes to measure co-morbidities, chronic pain, mental health conditions, and substance use; and study confounding (moderate 14, high 10) owing to lack of adjustment for index opioid prescription factors (dose, days' supply, type) which are expected to vary across patients and need to be controlled for. Detailed risk of bias assessment is presented in Appendix 2F and 2N.

Risk of prolonged opioid use

Overall, for opioid-naive patients who newly filled or received a prescription of opioids for surgery, the pooled risk for prolonged opioid use was 6% (95% CI 4% to 9%; 25 studies with 26 cohorts including 2,037,051 subjects; moderate-certainty evidence); for injury was 9% (95% CI 6% to 12%; 11 studies with 12 cohorts including 1,256,023 subjects; moderate-certainty evidence); and for dental pain was 3% (95% CI 2% to 6%; 4 studies including 76,915 subjects; high-certainty evidence). The proportion differed across surgery type groups, ranging from <0.5% in obstetrics and gynecology surgery to 16% in surgery for trauma – see Figure 2-2. In both the surgery and injury groups, studies that measured prolonged use in the intermediate term follow up reported higher proportions compared to long-term follow up – see Table 2-2 for details, and Figure 2-2 for a visual summary. Study-level results are available in Appendix 2-K.

Risk factors

Of the 35 included studies, 29 provided data that was usable for risk factor analyses[19-23,25-34,39-43,46-53] . Most studies (21/29) reported odds ratios as the measure of association between risk factors and prolonged use. A summary of findings is presented in Table 2-3 and results are summarized visually in Figure 2-3.

Sociodemographic factors

There were five baseline sociodemographic risk factors for which information was available in included studies: age, sex, race, level of education, and median household income. We found moderate-certainty evidence that there is no association between age and prolonged opioid use, with age measured as a continuous variable (narrative synthesis: two studies[28,50]; meta-analysis: three studies with seven cohorts, 64,615 subjects: OR 1, 95% CI 0.99 to 1.01) as well as a categorical variables comparing ≥60 years to 18 – 34 years (narrative synthesis: six studies[19-21,30,33,53]; meta-analysis: ten studies including 1,620,118 subjects: OR 1.08, 95% CI 0.89 to 1.30).

We also found high-certainty evidence that compared to subjects who were white, a higher risk of prolonged opioid use is observed for Black subjects (OR 1.24, 95% CI 1.19 to 1.29), a lower risk for Asian subjects (OR 0.79, 95% CI 0.72 to 0.86), and no difference in risk for Hispanic subjects (OR 0.98, 95% CI 0.94 to 1.03); data was derived from six studies including 530,664 subjects. We found low-certainty evidence that females have a slightly higher risk of prolonged use compared to males, and that those with only a high school diploma have a higher risk of prolonged opioid use compared to those with a college degree. Finally, we found low-certainty evidence that household income is not associated with prolonged use – see Table 2-3 for details.

History of co-morbidity and chronic pain conditions

We found high-certainty evidence that having a higher co-morbidity index score and a history of arthritis are associated with higher risk of prolonged use: co-morbidity index score (seven studies with 11 cohorts, 1,118,235 subjects: OR 1.07 95% CI 1.03 to 1.11); arthritis (eight studies, 1,265,215 subjects: OR 1.22, 95% CI 1.12 to 1.32). We also found moderate-certainty evidence and that those with a history of back pain and neck

pain have a higher risk of prolonged use: back pain (eight studies, 1,265,215 subjects: OR 1.25, 95% CI 1.14 to 1.36); neck pain (seven studies, 1,185,088 subjects: OR 1.12, 95% CI 1.06 to 1.17).

History of mental health conditions

We found high-certainty evidence that having a history of anxiety or depression is associated with a higher risk of prolonged use: anxiety (narrative synthesis: four studies; meta-analysis: seven studies with 11 cohorts, 1,145,022 subjects: OR 1.22, 95% CI 1.15 to 1.30); depression (narrative synthesis: four studies; meta-analysis: 13 studies with 17 cohorts, 1,763,427 subjects: OR 1.41, 95% CI 1.28 to 1.56). We found low-certainty evidence showing no association between psychosis and prolonged use – see Table 2-3 for details.

History of substance use

We found high-certainty evidence that subjects with a history of illicit-drug use have a higher risk of prolonged use compared to those without (narrative analysis: two studies; meta-analysis: 11 studies with 15 cohorts, 1,562,034 subjects: OR 1.55, 95% CI 1.31 to 1.83), and moderate certainty evidence for history of alcohol and tobacco use: alcohol (seven studies, 1,562,034 subjects: OR 1.38, 95% CI 1.20 to 1.59); tobacco (narrative synthesis: three studies; meta-analysis: five studies, 1,092,932 subjects: OR 1.47, 95% CI 1.24 to 1.75). We rated the evidence on marijuana use, which found no association, to be of very low-certainty – see Table 2-3.

First-prescription factors

There were three first-prescription factors that were selected a-priori for which information was presented in the included studies but was not sufficiently similar to pool estimates: average daily dose, days' supply, and type of first-prescription; and two factors that were reported in over three included studies for which data was sufficiently similar to pool: total perioperative morphine milligram equivalents (MME), and pre-operative opioid fill. We found moderate-certainty evidence that patients who receive prescriptions for long-acting opioids and for tramadol have a higher risk of prolonged use compared to those who receive short-acting opioids (narrative synthesis for both factors derived from: three studies, 1,272,760 subjects: two studies showed higher risk for both factors, and one showed no association between both factors and prolonged use after adjusting for total MME). We found moderate-certainty evidence that for those who are newly starting opioids for surgery, receiving ≥ 75th percentile of the total MME is associated with a higher risk for prolonged use (five studies, 1,101,032 subjects: OR 1.36, 95% CI 0.96 to 1.92). We assessed the evidence on average daily dose, total MME, and days' supply of the first prescription, as well as pre-operative opioid filling, to be of low to very low certainty – see Table 2-3 for details.

Sensitivity analyses

For incidence, including only studies that measured continuous or frequent use in the follow-up period, defined as a minimum of two or more opioid fills (or prescriptions or self-reported use), or a minimum of 90 days' supply, the risk of prolonged use dropped by one percentage point in each acute pain group. For risk factors, sensitivity analyses showed that results were robust to the potential impact of including studies with measures of co-morbidities, mental health conditions, and substance use that included mixed codes;

of including studies across all adjustment levels (suboptimal, sufficient, ideal); and of including studies at high risk of bias in the main analysis. We found similar results after we excluded those studies – see Appendix 2-M for results of sensitivity analyses.

2.3.5 Discussion

We found in this review that among opioid naive patients starting opioids for acute pain, 3% transition to prolonged opioid use following use for dental pain, 6% following surgery, and 9% following injury-related pain. This proportion differed by surgery subspecialty - ranging from 0% to 16%, and by timing of outcome measurement (8% at 60 - 180 days, and 4% beyond 180 days in the surgery group; 11% at 60 – 180 days, and 7% beyond 180 days in the injury group) . Importantly, our review shows that there is high-certainty evidence that race and ethnicity, co-morbidity status, a history of arthritis, anxiety, depression, and illicit drug use are all associated with a statistically significant higher risk of prolonged opioid use among opioid naive patients. We also found moderate-certainty evidence that having a history of back pain, neck pain, tobacco use, and alcohol use, as well as receiving a first-prescription of long-acting opioids or tramadol are all also associated with a statistically significant increased risk of prolonged use.

Our estimates of the risk of prolonged use fall mid-point in a range of findings previously presented in reviews that analyzed data on subgroups of opioid-naive patients newly starting opioids for surgical and injury-related pain, ranging from 4.1% to 10.4% in the intermediate-term to 2.6% to 10.9% in the long-term.[8-10] The two reviews that analyzed prolonged use in the intermediate- and long-term found that the reported proportion is lower in studies that measured prolonged use in the long-term, which is

consistent with our findings.[9,10] It is unclear whether this finding reflects genuine discontinuation of use for some patients in the long-term, or a shift to other avenues for supply (e.g. through diverted prescription opioids from friends or family, illicitly manufactured opioids).

Our finding that a higher risk of prolonged opioid use is observed among those with a history of drug, tobacco, and alcohol use is consistent with findings from previous reviews. [9,12 6, 50) 12] The lack of association between age, particularly older age, and prolonged opioid use in this review was derived from studies, the majority of which, adjusted for co-morbidities, chronic pain, and mental health conditions. Because these conditions are more prevalent in older age, our findings may support the hypothesis that the observed association between older age and prolonged use seen in some studies is due to confounding by these conditions.

Although it is not currently clear what reasons motivate patients to continue filling prescription opioids beyond the short-term period, some studies suggest that having pre-existing or persistent pain, or developing a new opioid use disorder may be two plausible explanations. For example, Delgado et al. found that many of the opioid-naive patients who newly started opioids for an ankle sprain and continued to use them did so for chronic unrelated pain conditions.[27] On the other hand, many of the risk factors that have been identified in this study, including having a history of chronic pain, substance use, anxiety, and depression, overlap with those that have been shown to be associated with risk of opioid misuse and opioid use disorder in opioid-naive populations. This suggests that there could be a possibility that prolonged use may be a surrogate for opioid use disorder in a subset of patients. [54] It is important to note, however, that factors

like younger age and male sex were found to be associated with higher risk of opioid misuse, but our findings did not identify them as important factors.[55]

Our findings show that individuals who were Black are at higher risk of prolonged use compared to those who were White, and that lower education is associated with prolonged use. Our findings on differences in risk of prolonged use by race should be interpreted cautiously. Racism is a structural determinant of health, and differences in health outcomes by race that are observed in large databases are often explained by racism rather than biological differences between races. [56,57] Black patients are less likely to be adequately treated for pain, which might exaggerate risk of prolonged use among those who are selectively chosen for treatment. Evidence indicates that racial biases in the treatment of pain and in the monitoring of patients on chronic opioid therapy already exist. [58,59] Compared to white patients, pain experienced by Black patients is less likely to be accurately measured or acknowledged leading to disparities in treatment. [59] Black patients are also less likely to be referred to a pain specialist. [58] The unexamined use of race in clinical tools and guidelines can result in withholding effective treatment from patients who need them based on racial bias rather than clinical justification, further perpetuating race-based health inequities.[57] Recognition of these issues is a first step towards exploring drivers of the observed higher risk of prolonged use among Black patients and finding avenues for risk mitigation, including better referral schemes to pain specialists when needed.

We suggest that based on our findings, more evidence is needed to reach a fuller understanding of the association between days' supply, average daily dose, and prolonged use in the studied population. Because these factors are modifiable, they carry

importance for clinical decision making. Our findings show that there is low-certainty evidence of no significant association between days' supply and very low-certainty evidence of no association between average daily dose and prolonged use. Included in the evidence underlying these findings is a large study by Shah et al. which showed significantly higher risk with longer days' supply and higher dose in mixed acute and chronic pain populations. [51] Furthermore, while certainty is very low, a consistent and dose-response relationship between total MME of first-filled prescription and prolonged opioid use was observed across multiple studies included in this review. The weakness of the evidence about total MME that was assessed included potential for risk of bias in studies and imprecision. This suggests further studies may be warranted for better understanding of risk for this factor. Our findings that being prescribed tramadol and long-acting opioids is associated with a higher risk of prolonged use are in keeping with current recommendations against prescribing long-acting opioids for acute pain and for opioid-naive patients. In general, when interpreting the association between first-prescription factors and prolonged use, it may be necessary to consider how the different opioid-specific factors - type, dose, days' supplied - interact or are correlated, and subsequently how that may affect the observed risks. In one of the included studies, Basilico et al. found that after adjusting for total MME of first-prescription, opioid type was no longer associated with prolonged use in orthopedic surgery patients.[34]

Strengths and limitations

One of the main strengths of this review is that we focused exclusively on studies of opioid-naive populations newly starting opioids for acute pain. This helped to keep the populations homogenous and provided us with a more reliable estimate of prolonged use.

In addition, our approach helped to eliminate the potential confounding effect of chronic pre-existing opioid use on the association between other risk factors of interest and prolonged opioid use. Another strength of this review is that most of the included studies used large, longitudinal databases, which are objective, complete, and ideal for prescription opioid safety research.[60] Finally, in the overall certainty in evidence assessment, we considered risk of bias for each risk factor individually rather than relying on one general risk of bias assessment for each study. This allowed us to give a more transparent and reliable reflection of the state of the current evidence for each factor.

Some limitations must be noted. We note high I^2 values and evidence of potential clinical heterogeneity in some of the meta-analyses presented. It has been recommended however not to rely on high I^2 values as evidence of important heterogeneity in meta-analyses of primary studies that include large databases as estimates of event rates are often highly precise due to the large sample sizes included leading to potentially misleading high I^2.[18] However, clinical heterogeneity may still exist among surgical populations by subspecialty and injury/ED groups, and results from subgroup analyses support this hypothesis. It is perhaps important to explore additional reasons for heterogeneity amongst these populations and consider not pooling data by presenting results separately for meaningful subgroups. Another limitation is missing assessments in included studies of the validity and reliability of risk factor measures that relied on routinely collected administrative databases. However, because these databases, and the selection of subjects into the study cohorts, ensured that the same setting and method of measurement are used for all subjects, and because of the completeness of risk factor data, the overall bias is likely to be minimal. Finally, the small number of studies

investigating first-prescription factors limited our ability to draw strong conclusions about these factors, which are important for making clinical recommendations.

Implications

The opioid-naive population is of particular interest because unlike for patients on chronic opioid therapy, primary prevention of prolonged use is achievable.[61] The findings from this review support the argument that opioid prescribing for acute pain to previously opioid-naive patients may be an important segue to unintended prolonged use. While our review finds that the baseline risk for this population across pain groups falls mostly below 10%, this proportion still translates to millions of patients in the real world who are transitioning into prolonged use. For future studies, it may be important to consider whether prolonged use is being used as a surrogate outcome for other, likely more important, opioid related harms, and to attempt to measure the latter when possible. [62] Indicators of opioid-related harms can be captured in the administrative and insurance claims databases that have been used in many of the included studies, and death can be captured through data-linkage. The evidence found in this review can help in the development of clinical practice guidelines, as well as in the selection of variable in clinical prediction models, to support more judicious opioid prescribing to this population.

Conclusion

Prolonged opioid use is an important potential consequence of new opioid prescribing for opioid-naive patients with acute pain. Balancing the expected benefits of pain relief with the potential harms of prolonged use is imperative when considering new opioid prescribing for this population. The increased risk of prolonged use that is

associated with having a history of substance use (drug, tobacco, or alcohol), a history of depression or anxiety, a history of multiple co-morbidities or chronic pain; and with receiving tramadol or long-acting opioids in the first-prescription all warrant careful assessment of who receives opioids for acute pain, and what is being prescribed in the first-prescription. The higher risk of prolonged use in patients who are Black and who have lower levels of education, warrants consideration of the role of racism and other root causes of inequities in the development of unintended outcomes in these potentially vulnerable groups of patients.

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Table 2-1: Distribution of risk of bias assessment ratings

	Risk ROB (n=35)				Risk factor measures of association ROB (n=29)						
Rating	**Study Participation**	**Study attrition**	**Outcome measurement**	**Overall**	**Study participation**	**Study attrition**	**Prognostic (risk) factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis and reporting**	**Overall**
Low	27	26	27	23	25	22	9	22	5	21	0
Moderate	5	8	6	9	2	6	20	5	14	5	18
High	3	1	2	3	2	1	0	2	10	3	11

Table 2-2: Summary of Findings; Risk of Prolonged Opioid Use (n= 35 studies)

Population: Opioid-naive adult patients newly starting opioids for acute pain: : (a) surgery, (b) trauma, injury, or ED presenting pain, (c) dental pain or procedures, (d) other.

Outcome: Prolonged opioid use.

			# studies (# participants)	Pooled Risk (95% CI)	GRADE Overall Rating
Surgery		**Overall**	25 with 26 cohorts (2,037,051)	6 (4 – 9)	+++ Due to inconsistency
	Subgroup: Surgery Type	Trauma Surgery	4 (56,466)	16 (3 – 36)	
		Obstetric/gynecologic surgery	2 (104,458)	0 (0 – 0)*	
		Plastic and reconstructive surgery	3 (74,673)	10 (5 – 15)	
		Mixed surgery	8 (1,617,321)	6 (2 – 13)	
		Thoracic surgery	1 (3,026)	14 (13 – 15)	
		Orthopedic surgery	8 (181,107)	3 (1 – 6)	
	Subgroup: Outcome Timing	Intermediate-term	15 (1,256,023)	8 (6 – 10)	
		Long-term	11 (781,028)	4 (3 – 6)	
Injury, trauma, or ED-presenting pain		**Overall**	11 with 12 groups* (1,256,023)	9 (6 – 12)	+++ Due to study limitations, due to inconsistency, due to potential publication bias
	Subgroups: Surgery status	With surgery	4 (56,466)	16 (3 – 36)	
		Without surgery	8 (912,224)	5 (3 – 8)	
	Subgroup: Outcome Timing	Intermediate-term	3 (24,908)	11 (6 – 18)	
		Long-term	9 (943,782)	7 (5 – 9)	
Dental pain or procedures		**Overall**	4 (76,915)	3 (2 – 6)	++++

ED Emergency Department

* ≤ 0.5% (Bateman 2016, 0.36%; Swenson 2018, 0.5%)

Overall certainty in the evidence: + very low; ++ low; +++ moderate; ++++ high

The risks reported in three studies of opioid-naive patients filling or receiving prescription opioids for other acute pain conditions were: 10% (95% CI 9% – 11%) following an initial prescription for acute pancreatitis, 17% (95% CI 13% – 23%) following prescription for curative intent radiation therapy for head and neck malignancies, and 35% (95% CI 34% – 36%) following an initial prescription for inflammatory bowel disease flare.[36,47,50]

Table 2-3: Summary of Findings; Estimates of Association between Risk factors and Prolonged Opioid Use. (n = 29 studies)

Population: Opioid-naive adult patients newly starting opioids for acute pain: : (a) surgery, (b) trauma, injury, or ED presenting pain, (c) dental pain or procedures, (d) other.
Outcome: Prolonged opioid use.

			Overall # studies reporting association*	Narrative analysis				Meta-analysis of adjusted estimates		Certainty in the evidence (GRADE)	
	Risk factor	Category	# studies, # cohorts	No. studies (# higher, neutral, lower risk)	+	0	-	# studies, # cohorts (# subjects)	Odds ratio (95% CI)	Overall Rating	Reason(s) for downgrading, if applicable
Sociodemographic factors	Age (continuous, years)	Continuous, years	5, 9	2	0	2	0	3, 7 (64,615)	1 (0.99 – 1.01)	+++	Due to study limitations
	Age	≥ 60 y vs. 18-34 y	16	6	0	3	3	10 (1,620,118)	1.08 (0.89 – 1.30)	+++	Due to inconsistency
	Sex	Female vs. male	20	7	0	6	1	13, 17 (1,674,203)	1.06 (1.00 – 1.13)	++	Due to study limitations, due to inconsistency, due to potential publication bias
	Race (Black)	Black vs. white	6	0	0	0	0	6 (530,644)	1.24 (1.19 – 1.29)	++++	-
	Race (Asian)	Asian vs. white	6	0	0	0	0	6 (530,644)	0.79 (0.72 – 0.86)	++++	-
	Race (Hispanic)	Hispanic vs. white	6	0	0	0	0	6 (530,644)	0.98 (0.94 – 1.03)	++++	-
	Education	HS vs. college degree	3	0	0	0	0	3 (53,897)	1.23 (1.02 – 1.48)	++	Due to study limitations, due to potential publication bias
	Income	MHI < 40K vs. ≥ 70K	7, 11	1	0	0	1	6, 7 (255,688)	1.21 (0.91 – 1.60)	++	Due to study limitations, due to imprecision
History of co-morbidity and chronic pain conditions	Comorbidity (continuous, no.)	Continuous	7, 11	0	0	0	0	7, 11 (1,118,235)	1.07 (1.03 – 1.11)	++++	-
	Comorbidity (categorical)	>3 vs. 0	4	0	0	0	0	4 (104,421)	1.53 (1.05 – 2.24)	++	Due to study limitations, due to inconsistency
	Back pain	Y vs. N	9	1	0	1	0	8 (1,265,215)	1.25 (1.14 – 1.36)	+++	Due to potential publication bias
	Arthritis	Y vs. N	9	1	0	1	0	8 (1,610,931)	1.22 (1.12 – 1.32)	++++	-
	Neck pain	Y vs. N	7	0	0	0	0	7 (1,185,088)	1.12 (1.06 – 1.17)	+++	Due to potential publication bias
History of mental health conditions	Anxiety	Y vs. N	11, 15	4	2	2	0	7, 11 (1,145,022)	1.22 (1.15 – 1.30)	++++	-
	Depression	Y vs. N	17, 20	4	3	1	0	13, 17 (1,763,427)	1.41 (1.28 – 1.56)	++++	-
	Psychosis	Y vs. N	7	1	0	1	0	6 (650,878)	1.11 (0.82 – 1.50)	+	Due to study limitations, due to imprecision, due to potential publication bias
History of substance use	Tobacco	Y vs. N	8	3	2	1	0	5 (1,092,932)	1.47 (1.24 – 1.75)	+++	Due to potential publication bias
	Alcohol	Y vs. N	8	1	0	1	0	7 (1,562,034)	1.38 (1.20 – 1.59)	+++	Due to potential publication bias
	Drugs	Y vs. N	13, 17	2	2	0	0	11, 15 (1,739,732)	1.55 (1.31 – 1.83)	++++	-

	Marijuana	Y vs. N	2	2	0	2	0	0	NA	+	Due to study limitations, due to imprecision, due to potential publication bias
Baseline opioid prescription factors	**Average DD of first prescription**	Various	2	2	1	1	0	0	NA	+	Due to study limitations, due to inconsistency, due to imprecision, due to potential publication bias
	Total MME of first-prescription	Various	3	3	3	0	0	0	NA	+	Due to study limitations, due to imprecision, due to potential publication bias
	Days' supply of first prescription	Various	3	3	1	2	0	0	NA	++	Due to imprecision, due to potential publication bias
	Opioid type of first prescription	Long- vs. short-acting	3	3	2	1	0	0	NA	+++	Due to potential publication bias
	Opioid type of first prescription	Tramadol vs. other	3	3	2	1	0	0	NA	+++	Due to potential publication bias
	Total perioperative MME	≥ 75th percentile vs. below	5	0	0	0	0	5 (1,101,032)	1.36 (0.96 – 1.92)	+++	Due to study limitations
	Preoperative opioid fill	Y vs. N	6, 10	0	0	0	0	6, 10 (1,153,983)	1.49 (1.27 – 1.73)	+	Due to study limitations, due to inconsistency, due to potential publication bias

OR odds ratio; CI confidence interval; Y yes; N no; HS High School; MHI Median Household Income; DD Daily Dose; NA not applicable because none available for pooling

*Adjusted prioritized – unadjusted only included when adjusted estimates were not reported.

Overall certainty in the evidence: + very low; ++ low; +++ moderate; ++++ high

Figure 2-1: PRISMA flow diagram for study identification, screening, and selection.

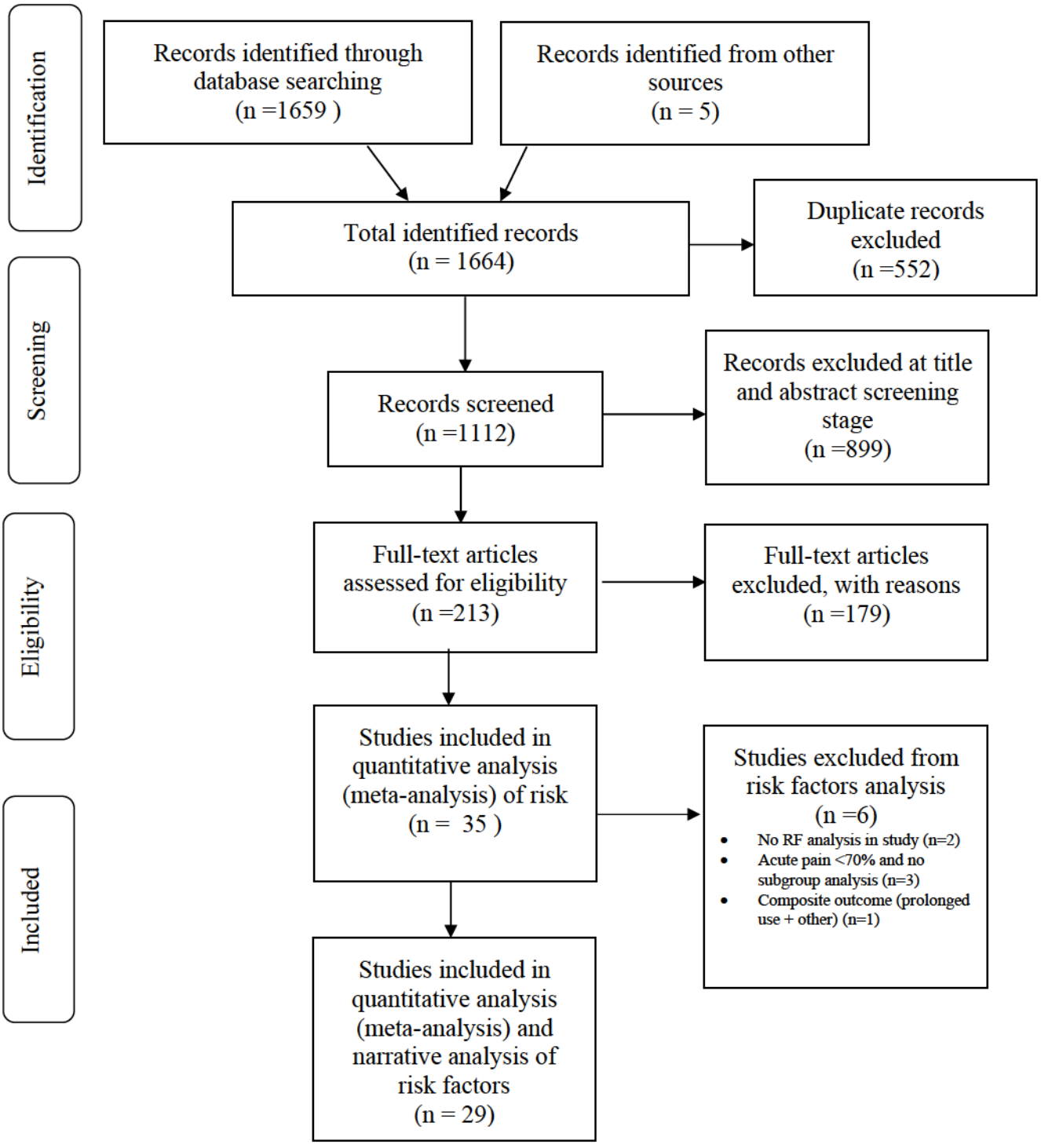
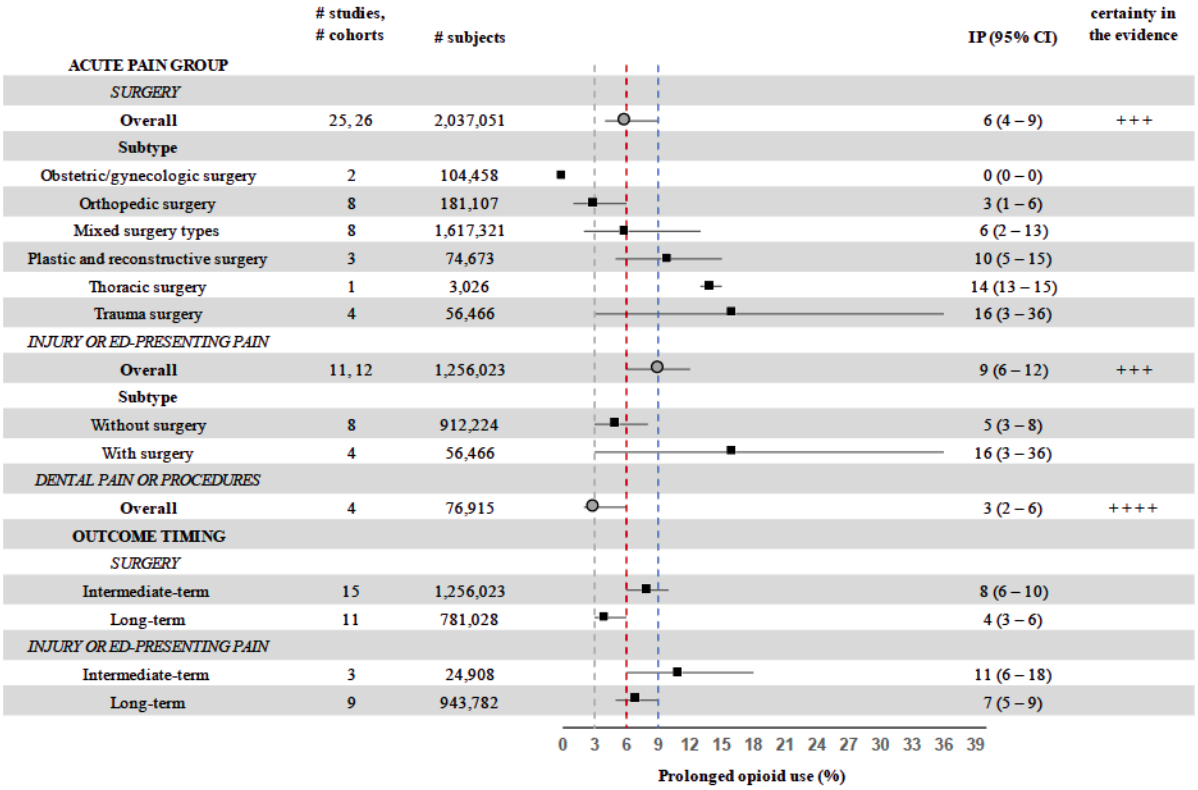


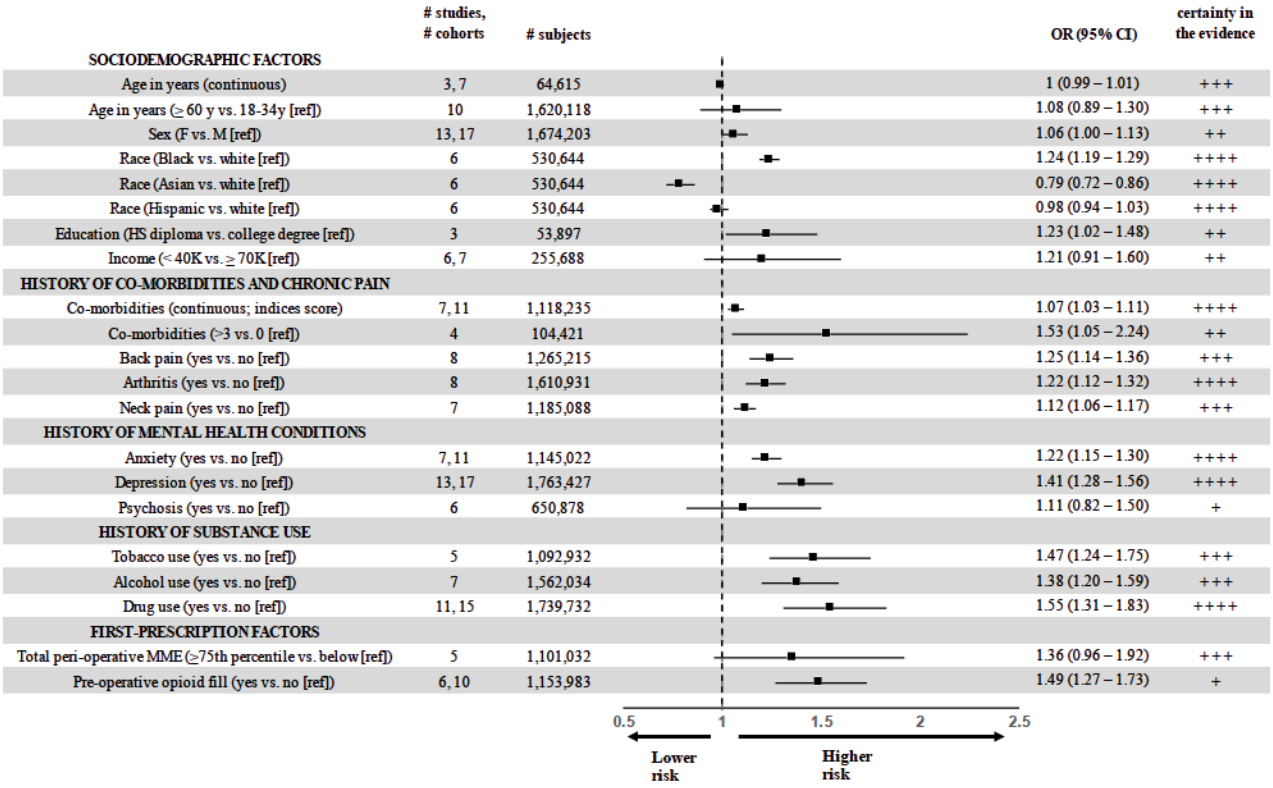
Figure 2-2: Pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



	# studies, # cohorts	# subjects	IP (95% CI)	certainty in the evidence
ACUTE PAIN GROUP				
SURGERY				
Overall	25, 26	2,037,051	6 (4 – 9)	+++
Subtype				
Obstetric/gynecologic surgery	2	104,458	0 (0 – 0)	
Orthopedic surgery	8	181,107	3 (1 – 6)	
Mixed surgery types	8	1,617,321	6 (2 – 13)	
Plastic and reconstructive surgery	3	74,673	10 (5 – 15)	
Thoracic surgery	1	3,026	14 (13 – 15)	
Trauma surgery	4	56,466	16 (3 – 36)	
INJURY OR ED-PRESENTING PAIN				
Overall	11, 12	1,256,023	9 (6 – 12)	+++
Subtype				
Without surgery	8	912,224	5 (3 – 8)	
With surgery	4	56,466	16 (3 – 36)	
DENTAL PAIN OR PROCEDURES				
Overall	4	76,915	3 (2 – 6)	++++
OUTCOME TIMING				
SURGERY				
Intermediate-term	15	1,256,023	8 (6 – 10)	
Long-term	11	781,028	4 (3 – 6)	
INJURY OR ED-PRESENTING PAIN				
Intermediate-term	3	24,908	11 (6 – 18)	
Long-term	9	943,782	7 (5 – 9)	

IP risk
Dashed lines indicated overall pooled estimates for the acute pain groups.
Overall certainty in the evidence: + very low; ++ low; +++ moderate; ++++ high
To calculate each of the summary proportions, we conducted random effects meta-analysis using Freeman-Tukey Double Arcsine Transformation (Freeman, M. F. , and Tukey, J. W. 1950) to stabilize variances. The inverse of the variance of the risk for each study was used to assign weights. The calculation approach rounds proportions that are below 0.05% down to 0%.
Intermediate-term 60 – 180 days; Long-term > 180 days

Figure 2-3: Pooled odds ratios (with 95% CI) estimating the association between patient characteristics, first-prescription factors, and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis)



	# studies, # cohorts	# subjects	OR (95% CI)	certainty in the evidence
SOCIODEMOGRAPHIC FACTORS				
Age in years (continuous)	3, 7	64,615	1 (0.99 – 1.01)	+++
Age in years (≥ 60 y vs. 18-34y [ref])	10	1,620,118	1.08 (0.89 – 1.30)	+++
Sex (F vs. M [ref])	13, 17	1,674,203	1.06 (1.00 – 1.13)	++
Race (Black vs. white [ref])	6	530,644	1.24 (1.19 – 1.29)	++++
Race (Asian vs. white [ref])	6	530,644	0.79 (0.72 – 0.86)	++++
Race (Hispanic vs. white [ref])	6	530,644	0.98 (0.94 – 1.03)	++++
Education (HS diploma vs. college degree [ref])	3	53,897	1.23 (1.02 – 1.48)	++
Income (< 40K vs. ≥ 70K [ref])	6, 7	255,688	1.21 (0.91 – 1.60)	++
HISTORY OF CO-MORBIDITIES AND CHRONIC PAIN				
Co-morbidities (continuous; indices score)	7, 11	1,118,235	1.07 (1.03 – 1.11)	++++
Co-morbidities (>3 vs. 0 [ref])	4	104,421	1.53 (1.05 – 2.24)	++
Back pain (yes vs. no [ref])	8	1,265,215	1.25 (1.14 – 1.36)	+++
Arthritis (yes vs. no [ref])	8	1,610,931	1.22 (1.12 – 1.32)	++++
Neck pain (yes vs. no [ref])	7	1,185,088	1.12 (1.06 – 1.17)	+++
HISTORY OF MENTAL HEALTH CONDITIONS				
Anxiety (yes vs. no [ref])	7, 11	1,145,022	1.22 (1.15 – 1.30)	++++
Depression (yes vs. no [ref])	13, 17	1,763,427	1.41 (1.28 – 1.56)	++++
Psychosis (yes vs. no [ref])	6	650,878	1.11 (0.82 – 1.50)	+
HISTORY OF SUBSTANCE USE				
Tobacco use (yes vs. no [ref])	5	1,092,932	1.47 (1.24 – 1.75)	+++
Alcohol use (yes vs. no [ref])	7	1,562,034	1.38 (1.20 – 1.59)	+++
Drug use (yes vs. no [ref])	11, 15	1,739,732	1.55 (1.31 – 1.83)	++++
FIRST-PRESCRIPTION FACTORS				
Total peri-operative MME (≥75th percentile vs. below [ref])	5	1,101,032	1.36 (0.96 – 1.92)	+++
Pre-operative opioid fill (yes vs. no [ref])	6, 10	1,153,983	1.49 (1.27 – 1.73)	+

OR odds ratio; CI confidence interval; F female; M male; HS high school
Overall certainty in the evidence: + very low; ++ low; +++ moderate; ++++ high

2.5 Appendices

Appendix 2-A Further Study Selection Specifications

PICOT* Category	Criteria	
Population	To be eligible for inclusion, a study must have has a population of adult opioid-naive patients who received or filled an opioid prescription for acute pain.	
	Adult	We considered studies that included both adults and children if a. At least 70% of subjects were 18 years or older, or b. The authors report the results of an analysis of the subgroup of adult subjects.
	Opioid-naive	We considered studies with a mixed population of opioid-naive and non-opioid-naive subjects if: a. At least 70% of subjects were opioid-naive; or b. The authors report the results of an analysis of the subgroup of opioid-naive subjects. We defined opioid-naivety as no opioid use for at least 30 days before the index prescription measured by self-reports, documented fills in medical claims, or documented prescriptions in medical records. We also accepted definitions of no use for 11 months until 30 days before a surgical operation.
	Acute pain	We considered studies that included a mixed pain population (acute and chronic) or a population of patients presenting to both acute and non-acute care settings if a. At least 70% of the study population had acute pain or presented to an acute care setting or b. The authors report the results of an analysis of the subgroup of subjects with acute pain or who presented to the acute care setting. Although not all patients presenting to the acute care setting will be free of chronic pain, opioids prescribed in this setting will often target acute exacerbations or anticipated postoperative pain.
	Opioid filling	We considered studies that included patients who did not receive opioids at baseline, like studies of patients undergoing procedures for which opioid prescriptions are written routinely, if a. The majority (70% +) of subjects received or filled an opioid prescription or b. The authors report the results of an analysis of the subgroup of subjects who received opioids.
Outcome	To be eligible for selection, a study must have assessed prolonged opioid use by reporting either a measure of receiving an opioid prescription or dispensing opioids at or beyond 60 days from the day of an index prescription receipt or fill, or acute pain diagnosis. Subsequently, any of the following minimum measurement requirements, if reported, would deem a study eligible for inclusion: (a) any fills at or beyond 60 days, (b) continuous filling from the day of the index prescription up to 60 days or longer, (c) a number of fills in the follow-up period that likely exceeds 60 days in supply, or (d) a pill count that is equivalent to at least 60 days' supply.	
Time (follow-up)	Minimum of 60 days from date of receiving or filling an index prescription or acute pain diagnosis.	
Exposure (risk factors)	For studies that did not fully (i.e. 100%) meet all the population criteria, an assessment of any patient and/or prescription factor(s) must have been presented in the study to be included.	

*The Intervention and Comparison categories do not apply to this systematic review because it is a review of risk factors.

Appendix 2-B Search strategies

1. Database: PsycINFO

#	Query
S11	S7 AND S10
S10	S8 AND S9
S9	S3 OR S4 OR S5 OR S6
S8	S1 OR S2
S7	TI(("long term" OR "longer term" OR prolonged OR chronic OR persistent OR late OR longitudinal OR continue*) N2 us*) OR AB(("long term" OR "longer term" OR prolonged OR chronic OR persistent OR late OR longitudinal OR continue*) N2 us*) OR TI((failure OR time) N2 discontin*) OR AB((failure OR time) N2 discontin*)
S6	TI ("dentist*" or "oral hygien*" or "dental hygien*" or "oral health" or "dental") OR AB ("dentist*" or "oral hygien*" or "dental hygien*" or "oral health" or "dental")
S5	TI (("post-surg*" or "post-op*" or "surg*" or "ortho*" or "arthro*") OR AB (("post-surg*" or "post-op*" or "surg*" or "ortho*" or "arthro*")
S4	TI ((acute or "short term") N2 pain) OR AB ((acute or "short term") N2 pain)
S3	TI (("injur*" or "trauma*" or "work-related" or "occupation*" or "emergency") N2 pain) OR AB (("injur*" or "trauma*" or "work-related" or "occupation*" or "emergency") N2 pain)
S2	TI (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol) OR AB (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol) OR MW (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol)
S1	DE "Opiates" OR DE "Buprenorphine" OR DE "Codeine" OR DE "Endogenous Opiates" OR DE "Fentanyl" OR DE "Heroin" OR DE "Morphine" OR DE "Papaverine"

2. Database: CINAHL

#	Query
S11	S7 AND S10
S10	S8 AND S9
S9	S3 OR S4 OR S5 OR S6
S8	S1 OR S2
S7	TI(("long term" OR "longer term" OR prolonged OR chronic OR persistent OR late OR longitudinal OR continue*) N2 us*) OR AB(("long term" OR "longer term" OR prolonged OR chronic OR persistent OR late OR longitudinal OR continue*) N2 us*) OR TI((failure OR time) N2 discontin*) OR AB((failure OR time) N2 discontin*)
S6	TI ("dentist*" or "oral hygien*" or "dental hygien*" or "oral health" or "dental") OR AB ("dentist*" or "oral hygien*" or "dental hygien*" or "oral health" or "dental")
S5	TI ("injur*" or "trauma*" or "work-related" or "occupation*" or "emergency") N2 pain) OR AB ("injur*" or "trauma*" or "work-related" or "occupation*" or "emergency") N2 pain)
S4	TI (("post-surg*" or "post-op*" or "surg*" or "ortho*" or "arthro*") OR AB (("post-surg*" or "post-op*" or "surg*" or "ortho*" or "arthro*")
S3	TI (acute or short term N2 pain) OR AB (acute or short term N2 pain)
S2	TI (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol) OR AB (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol) OR MW (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol)
S1	MH "Analgesics, Opioid"

3. Database: EMBASE

No.	Query
#13	((((('long term' OR 'longer term' OR prolonged OR chronic OR persistent OR late OR longitudinal OR continue*) NEAR/2 (use* OR usage OR using)):ti,ab,kw) OR ((failure NEAR/2 discontin*):ti,ab,kw) OR ((time NEAR/2 discontin*):ti,ab,kw)) AND ((('dentist*':ti,ab,kw OR 'oral hygien*':ti,ab,kw OR 'dental hygien*':ti,ab,kw OR 'oral health':ti,ab,kw OR 'dental':ti,ab,kw) OR ('dentistry'/exp OR 'mouth hygiene'/exp)) OR (('post-surg*' OR 'post-op*' OR 'surg*' OR 'ortho*' OR 'arthro*' OR postop*) NEAR/2 (pain OR analgesi* OR anesthe* OR anaesthe*)):ti,ab,kw OR (('injur*' OR 'trauma*' OR 'work-related' OR 'occupation*' OR 'emergency' OR acute OR 'short term') NEAR/2 pain):ti,ab,kw OR 'posttraumatic pain'/exp) AND ((alfentanil:ti,ab,kw OR alphaprodine:ti,ab,kw OR 'beta casomorphin*':ti,ab,kw OR buprenorphine:ti,ab,kw OR carfentanil:ti,ab,kw OR codeine:ti,ab,kw OR deltorphin:ti,ab,kw OR dextromethorphan:ti,ab,kw OR dezocine:ti,ab,kw OR dihydrocodeine:ti,ab,kw OR dihydromorphine:ti,ab,kw OR enkephalin*:ti,ab,kw OR ethylketocyclazocine:ti,ab,kw OR ethylmorphine:ti,ab,kw OR etorphine:ti,ab,kw OR fentanyl:ti,ab,kw OR heroin:ti,ab,kw OR hydrocodone:ti,ab,kw OR hydromorphone:ti,ab,kw OR ketobemidone:ti,ab,kw OR levorphanol:ti,ab,kw OR lofentanil:ti,ab,kw OR meperidine:ti,ab,kw OR meptazinol:ti,ab,kw OR methadone:ti,ab,kw OR 'methadyl acetate':ti,ab,kw OR morphine:ti,ab,kw OR nalbuphine:ti,ab,kw OR opium:ti,ab,kw OR oxycodone:ti,ab,kw OR oxymorphone:ti,ab,kw OR pentazocine:ti,ab,kw OR phenazocine:ti,ab,kw OR phenoperidine:ti,ab,kw OR pirinitramide:ti,ab,kw OR promedol:ti,ab,kw OR propoxyphene:ti,ab,kw OR remifentanil:ti,ab,kw OR sufentanil:ti,ab,kw OR tilidine:ti,ab,kw OR tapentadol:ti,ab,kw OR tramadol:ti,ab,kw OR diamorphine:ti,ab,kw OR diacetylmorphine:ti,ab,kw OR 'opioid*':ti,ab,kw OR 'opiate*':ti,ab,kw) OR 'narcotic analgesic agent'/exp)
#12	(alfentanil:ti,ab,kw OR alphaprodine:ti,ab,kw OR 'beta casomorphin*':ti,ab,kw OR buprenorphine:ti,ab,kw OR carfentanil:ti,ab,kw OR codeine:ti,ab,kw OR deltorphin:ti,ab,kw OR dextromethorphan:ti,ab,kw OR dezocine:ti,ab,kw OR dihydrocodeine:ti,ab,kw OR dihydromorphine:ti,ab,kw OR enkephalin*:ti,ab,kw OR ethylketocyclazocine:ti,ab,kw OR ethylmorphine:ti,ab,kw OR etorphine:ti,ab,kw OR fentanyl:ti,ab,kw OR heroin:ti,ab,kw OR hydrocodone:ti,ab,kw OR hydromorphone:ti,ab,kw OR ketobemidone:ti,ab,kw OR levorphanol:ti,ab,kw OR lofentanil:ti,ab,kw OR meperidine:ti,ab,kw OR meptazinol:ti,ab,kw OR methadone:ti,ab,kw OR 'methadyl acetate':ti,ab,kw OR morphine:ti,ab,kw OR nalbuphine:ti,ab,kw OR opium:ti,ab,kw OR oxycodone:ti,ab,kw OR oxymorphone:ti,ab,kw OR pentazocine:ti,ab,kw OR phenazocine:ti,ab,kw OR phenoperidine:ti,ab,kw OR pirinitramide:ti,ab,kw OR promedol:ti,ab,kw OR propoxyphene:ti,ab,kw OR remifentanil:ti,ab,kw OR sufentanil:ti,ab,kw OR tilidine:ti,ab,kw OR tapentadol:ti,ab,kw OR tramadol:ti,ab,kw OR diamorphine:ti,ab,kw OR diacetylmorphine:ti,ab,kw OR 'opioid*':ti,ab,kw OR 'opiate*':ti,ab,kw) OR 'narcotic analgesic agent'/exp
#11	'narcotic analgesic agent'/exp
#10	alfentanil:ti,ab,kw OR alphaprodine:ti,ab,kw OR 'beta casomorphin*':ti,ab,kw OR buprenorphine:ti,ab,kw OR carfentanil:ti,ab,kw OR codeine:ti,ab,kw OR deltorphin:ti,ab,kw OR dextromethorphan:ti,ab,kw OR dezocine:ti,ab,kw OR dihydrocodeine:ti,ab,kw OR dihydromorphine:ti,ab,kw OR enkephalin*:ti,ab,kw OR ethylketocyclazocine:ti,ab,kw OR ethylmorphine:ti,ab,kw OR etorphine:ti,ab,kw OR fentanyl:ti,ab,kw OR heroin:ti,ab,kw OR hydrocodone:ti,ab,kw OR hydromorphone:ti,ab,kw OR ketobemidone:ti,ab,kw OR levorphanol:ti,ab,kw OR lofentanil:ti,ab,kw OR meperidine:ti,ab,kw OR meptazinol:ti,ab,kw OR methadone:ti,ab,kw OR 'methadyl acetate':ti,ab,kw OR morphine:ti,ab,kw OR nalbuphine:ti,ab,kw OR opium:ti,ab,kw OR oxycodone:ti,ab,kw OR oxymorphone:ti,ab,kw OR pentazocine:ti,ab,kw OR phenazocine:ti,ab,kw OR phenoperidine:ti,ab,kw OR pirinitramide:ti,ab,kw OR promedol:ti,ab,kw OR propoxyphene:ti,ab,kw OR remifentanil:ti,ab,kw OR sufentanil:ti,ab,kw OR tilidine:ti,ab,kw OR tapentadol:ti,ab,kw OR tramadol:ti,ab,kw OR diamorphine:ti,ab,kw OR diacetylmorphine:ti,ab,kw OR 'opioid*':ti,ab,kw OR 'opiate*':ti,ab,kw
#9	(('dentist*':ti,ab,kw OR 'oral hygien*':ti,ab,kw OR 'dental hygien*':ti,ab,kw OR 'oral health':ti,ab,kw OR 'dental':ti,ab,kw) OR ('dentistry'/exp OR 'mouth hygiene'/exp)) OR (('post-surg*' OR 'post-op*' OR 'surg*' OR 'ortho*' OR 'arthro*' OR postop*) NEAR/2 (pain OR analgesi* OR anesthe* OR

	anaesthe*)):ti,ab,kw OR (('injur*' OR 'trauma*' OR 'work-related' OR 'occupation*' OR 'emergency' OR acute OR 'short term') NEAR/2 pain):ti,ab,kw OR 'posttraumatic pain'/exp
#8	'posttraumatic pain'/exp
#7	(('injur*' OR 'trauma*' OR 'work-related' OR 'occupation*' OR 'emergency' OR acute OR 'short term') NEAR/2 pain):ti,ab,kw
#6	(('post-surg*' OR 'post-op*' OR 'surg*' OR 'ortho*' OR 'arthro*' OR postop*) NEAR/2 (pain OR analgesi* OR anesthe* OR anaesthe*)):ti,ab,kw
#5	('dentist*':ti,ab,kw OR 'oral hygien*':ti,ab,kw OR 'dental hygien*':ti,ab,kw OR 'oral health':ti,ab,kw OR 'dental':ti,ab,kw) OR ('dentistry'/exp OR 'mouth hygiene'/exp)
#4	'dentistry'/exp OR 'mouth hygiene'/exp
#3	'dentist*':ti,ab,kw OR 'oral hygien*':ti,ab,kw OR 'dental hygien*':ti,ab,kw OR 'oral health':ti,ab,kw OR 'dental':ti,ab,kw
#2	((('long term' OR 'longer term' OR prolonged OR chronic OR persistent OR late OR longitudinal OR continue*) NEAR/2 (use* OR usage OR using)):ti,ab,kw) OR ((failure NEAR/2 discontin*):ti,ab,kw) OR ((time NEAR/2 discontin*):ti,ab,kw)
#1	((('long term' OR 'longer term' OR prolonged OR chronic OR persistent OR late OR longitudinal OR continue*) NEAR/2 us*):ti,ab,kw) OR ((failure NEAR/2 discontin*):ti,ab,kw) OR ((time NEAR/2 discontin*):ti,ab,kw)

4. Database: MEDLINE

	Search
1	Analgesics, Opioid*.mp.
2	(opiate* or opioid* or alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or diacetylmorphine or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol).tw.
3	1 or 2
4	exp Acute Pain/
5	((acute or "short term") adj2 pain).tw. OR ("post-surg*" or "post-op*" or "surg*" or "ortho*" or "arthro*").tw. OR (("injur*" or "trauma*" or "work-related" or "occupation*" or "emergency") adj2 pain).tw. OR ("dentist*" OR "oral hygien*" OR "dental hygien*" OR "oral health" OR "dental").tw.
6	4 or 5

7	((("long term" or "longer term" or prolonged or chronic or persistent or late or longitudinal or continue*) adj2 us*) or (failure adj2 discontin*) or (time adj2 discount*)).tw.
8	3 and 6
9	7 and 8

5. Database: Web of Science

	Search
#1	TS= (opiate* or opioid* or alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or diacetylmorphine or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol or tramadol)
#2	TS = (Acute Pain)
#3	TS=(((acute or "short term") NEAR/2 pain).tw. OR ("post-surg*" or "post-op*" or "surg*" or "ortho*" or "arthro*").tw. OR (("injur*" or "trauma*" or "work-related" or "occupation*" or "emergency") NEAR/2 pain).tw.) OR (“dentist*” OR “oral hygien*” OR “dental hygien*” OR “oral health” OR “dental”).tw.
#4	TS=((("long term" or "longer term" or prolonged or chronic or persistent or late or longitudinal or continue*) NEAR/2 (use* OR usage*)) or (failure NEAR/2 discontin*) or (time NEAR/2 discount*)).
#5	#3 OR #2
#6	#5 AND #1
#7	#6 AND #4

Appendix 2-C Screening Criteria

1. Is the study a retrospective or prospective cohort study, case-control study, or clinical trial? ☐ Yes ☐ No

2. Does the study include a population of:

   a. Either all subjects are adults OR a minimum of 70% adult (18 years and above) OR regardless of proportion, a separate analysis of adults was reported? ☐ Yes, all ☐ Yes, partial ☐ No

   b. Either all subjects are opioid-naive OR a minimum of 70% opioid-naive subjects OR regardless of proportion, a separate analysis of opioid-naive subjects was reported? ☐ Yes, all ☐ Yes, partial ☐ No

   c. Either all subjects have acute pain and/or presented to an acute care setting OR a minimum of 70% of subjects had acute pain and/or presented to an acute care setting OR regardless of proportion, a separate analysis of subjects with acute pain and/or in the acute care setting was reported?

      ☐ Yes, all ☐ Yes, partial ☐ No

   d. Either all subjects received an opioid prescription for acute pain (measured as receiving or filling a prescription immediately after or within a month from the acute pain episode) OR "the majority" received an opioid prescription as mentioned above OR a separate analysis of subjects who received a prescription as mentioned above was reported (regardless of proportion)? ☐ Yes, all ☐ Yes, partial ☐ No

3. Did the study assess prolonged opioid use either as a measure of receiving an opioid prescription or of dispensing opioids at or beyond 60 days (~ 2 months) from the index prescription?

   ☐ Yes ☐ No

If the answer to any of the questions above is NO, exclude study and do not proceed further.

If the answer to all of the questions is YES, include study.

If the answer to any of the questions is YES, PARTIAL, move to the next question.

4. Did the study assess the association between patient and/or prescription factors and prolonged opioid use?

   ☐ Yes ☐ No

If the answer is YES, include.

If the answer is NO, exclude.

Appendix 2-D Information about Data Extraction and Management

General

We developed an Excel data extraction form to extract pertinent data from each included study. We extracted data on the following: (1) Study characteristics including first author, year, country, setting, study design, sample size, data sources and time frame, and duration of follow up, (2) Study population including age, sex, percentage with acute pain, type of acute pain, % opioid-naive, definition of opioid-naivety, % who filled opioids at baseline, (3) Patient and prescription risk factors (RF), (4) Prolonged opioid use definition(s), (5) Type of outcome analysis performed, whether it was adjusted, and list of covariates, and (6) Outcome data for (a) The risk of the outcome and (b) The measures of association for included risk factors as a point estimate (odds ratio, relative risk, hazard ratio, or beta coefficient) and 95% confidence intervals, standard error, or exact p-value. If a study included risk data on subgroups belonging to more than one of the pre-determined acute pain groups, we extracted data for each of the groups separately. Some studies with populations of patients with acute and chronic pain presented subgroup data for risks but conducted RF analysis on the entire study population. In these studies, we extracted RF data only when a minimum of 70% of the population received their index opioid prescription for acute pain.

Risk factors

We identified a-priori the following eighteen factors for which data was extracted in this review, when available: baseline age, sex, race, education, income, work loss, history of depression, anxiety, and psychosis, history of co-morbidities, history of chronic pain conditions (low back pain, neck pain, and arthritis), drug use, alcohol use, tobacco

use, and marijuana use; and baseline first-prescription factors including dose, days' supply, and type of opioid prescribed. The choice of factors was guided by (1) conceptual considerations presented in Hooten et al.'s framework (Hooten 2017); (2) findings from previous studies that identified risk factors of importance; (3) risk-stratifiers presented in the Canadian opioid prescribing guideline (Busse 2017); and (4) expert opinion. We also considered other factors were assessed in studies but missed from our list.

We prioritized extracting data on adjusted estimates as recommended by Foroutan et al. (Foroutan 2020), and we rated the level of adequacy of statistical adjustment in each study as either (a) ideal, (b) minimum sufficient, or (c) suboptimal. To aid with adjustment adequacy assessment, we grouped co-variates of interest (i.e. potential confounders) into three groups: Group (a): Sociodemographic factors which were age, sex, race, education, income, and work loss; Group (b): Clinical factors which were a history of mental health conditions, a history of substance use/abuse, a history of chronic pain, and a history of any other comorbidity, and Group (c): The first-prescription characteristics which were opioid dose, days' supply, and type. We defined three levels of risk adjustment as follows: a. *Ideal adjustment* is an adjustment of a minimum of two factors from each group including at least one of a history of psychiatric illness or a history of substance abuse, b. *Minimum sufficient adjustment* is an adjustment of a minimum of one factor from each group, and c. *Suboptimal adjustment* is an adjustment of any factors within any of the groups without reaching minimum sufficient adjustment.

We switched reference groups when necessary to standardize comparisons. When results were presented in figures only, we approximated the values from the figures. We synthesized point estimates for age as a continuous variable and categorical variable

comparing the group closest to 65 year of age (lowest value threshold acceptable set at 55 years) with the group closest to 18 years (highest value threshold acceptable set at 45 years) as the reference category. For education, we compared the group with a high school diploma to the group with a college degree as the reference category. We selected the 'high school diploma' group, and not 'less than high school' group to ensure larger samples and higher precision in the pooled estimates. For income, we compared the group with median household income of <40K to the group with ≥70K as the reference group, with <50K as upper acceptable threshold and 60K as lowest acceptable threshold, respectively. For history of comorbidities, chronic pain, mental health conditions, and substance use, we considered as sufficiently similar measures of diagnostic codes in insurance claims and administrative databases, measures of clinical diagnosis notes in electronic or physical medical records, and measures of self-report of a history of the condition. For chronic pain, mental health conditions, and substance use we accepted measures with a combination of codes for more than one condition as sufficiently similar, excluding them in a sensitivity analysis later.

Outcome measure prioritization, bias assessment, and subgroup categorization

In studies that reported more than one measure of prolonged use, we selected the measure that was used to both report the risk and analyze associations with risk factors in the study. In situations where two or more measures were used in both reporting the risk and analyzing risk factors, we prioritized the measure that captured use for the longest period (up to 12 months) over one measuring use over a shorter period, and the measure capturing continuous or frequent filling over a measure capturing a minimum of one fill.

In risk of bias assessment, we assessed each outcome and labeled it as objective and unbiased if it met the following criteria: (a) baseline fill documented, (b) use at follow up measured using fills (as opposed to self-report or written prescriptions), (c) attempted to capture continuation of use (not a single fill) OR excluded subjects with subsequent healthcare encounters for which opioids could be prescribed, and (d) use was captured in the intermediate to long-term (3 – 12 months from first-prescription).

To aid with risk subgroup analysis, we mapped study outcomes to two subgroups according the outcome timing: (1) *Prolonged opioid use to intermediate term*, which we defined as use beyond 60 days (two months) and up to 180 days (six months) from the date of the index opioid prescription fill, and (2) *Prolonged opioid use to long-term*, which we defined as use from the index date. Outcomes that included a definition that *may* have included use to beyond 180 days were mapped to the latter group (for example, the following definition from Thiels 2019 "*an opioid use episode starting in the 180 days after surgery that spans at least 90 days and includes either 10 or more opioid fills or 120 or more days' supply of opioids*").

Acute pain group categorization

For the purposes for synthesizing the evidence on risk of prolonged opioid use for acute pain groups separately, we categorized every study included in the review into one of the following groups based on the indication(s) for which opioids were prescribed at baseline: (1) Surgery, (2) Injury, trauma, or emergency department presenting pain, or (3) Dental pain or procedures. Studies with subjects who had undergone any type of major or minor surgery, including caesarian section and surgery for trauma or injury, were considered to fulfill the criteria for *surgery*. Because evidence shows that the duration of

opioid use following surgery may be affected by the type of surgery that the patient underwent, we created the following surgery subspecialty subgroups: trauma including burns, obstetrics and gynecology, plastics, cardiothoracic, orthopedic, spine, and mixed surgery - the latter group included study populations who had undergone various surgical procedures including all surgical subspecialties such as abdominal, colorectal, head and neck, gynecological, plastics, vascular surgery. These subgroups were used in the analysis of risks for the surgery group.

Studies with subjects for whom opioids were prescribed for any type of emergency department presenting pain, injury including burns, or trauma, including injuries and trauma for which subjects underwent surgery are included in the *injury, trauma, or emergency department presenting pain*. If a study with a mixed pain population presented separate data from subjects that belong to more than one acute pain group, we included the data from the study in more than one group (for example, some data can be presented in the surgery group, while other data is presented in the dental pain group). Data for studies that met the criteria for more than one group were included in both (for example, studies that included subjects who underwent surgery for trauma were included in both the *surgery* group and the *injury, trauma, or emergency department presenting pain* groups). We included the remaining studies in a group labeled '*other acute pain'* if they included patients who filled opioids for acute pain that does not belong to any of the first three groups (for example, acute pain due to radiation therapy or acute flare ups of a chronic conditions such as inflammatory bowel disease), recognizing the possible heterogeneity of this group both within itself and across other acute pain groups. Acute pain groups were not used in the synthesis of risk factors; only acute pain as an overall group was of interest.

If a study included risk data on subgroups belonging to more than one of the pre-determined acute pain groups, we extracted data for each of the groups separately. Some studies with populations of patients with acute and chronic pain presented subgroup data for risks but conducted RF analysis on the entire study population. In these studies, we extracted RF data only when a minimum of 70% of the population received their index opioid prescription for acute pain

Appendix 2-E: Characteristics of included studies. (n=35)

	First Author Year	Country	Data Source (time frame)	Type of acute pain*	Sample size	Baseline age in years (mean (SD) or median (IQR) or distribution); % female; % opioid-naive	Prolonged opioid use definition**	Multiple measures of prolonged opioid use were reported: n, y (basis upon which outcome included in review was selected)	Included in RF analysis: y, n (reason)
1	AlDabbagh 2014	Sweden	Administrative Databases: National Hospital Discharge Register, Prescribed Drug Register, Total Population Register (2005 – 2008)	Surgery (Trauma) + Injury, Trauma, or ED presenting pain	639	Median age 45y (16-97); 39% female; 100% opioid-naive	Opioid use not ceased at 12 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months**	y (in studies that used the same outcome definition at multiple time points and a time-to-event analysis, we prioritized the definition measuring use at or closest to 12 months)	y
2	AlDabbagh 2016	Sweden	Administrative Databases: National Hospital Discharge Register, Prescribed Drug Register, Total Population Register (2005 – 2008)	Surgery (Trauma) + Injury, Trauma, or ED presenting pain	891	Median age 75y (16-102); 56% female; 100% opioid-naive	Opioid use not ceased at 12 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months**	y (in studies that used the same outcome definition at multiple time points and a time-to-event analysis, we prioritized the definition measuring use at or closest to 12 months)	y
3	Basilico 2019	United States	Institutional Databases and Research Patient Data Registry for two level-I trauma centres (2002 – 2015)	Surgery (Trauma) + Injury, Trauma, or ED presenting pain	17,961	Mean age 51.9y (18.4); 50% female, 100% opioid-naive	Prolonged opioid use, which was identified as the receipt of at least one opioid prescription within 90 days of injury presentation and another at 90 to 180 days postoperatively	n	y

4	Bateman 2016	United States	Nationwide Insurance Claims Database: Clinformatics Data Mart Database which includes data for outpatient pharmacy dispensings, inpatient and outpatient services, procedures and associated diagnoses from United-Healthcare (2003 – 2011)	Surgery (Obstetrics and Gynecology)	80,127	Age distribution: <20y (1.7%), 20-29y (32%), 30-39y (57.4%), ≥40 (8.9%); 100% female; 100% opioid-naive.	Persistent opioid use definition derived from trajectory models on opioid use in 12 months of follow up	n	y
5	Bennett 2018	United States	Nationwide Insurance Claims Database: Clinformatics Data Mart Database (2001 – 2015)	Surgery (Plastics)	11,257	Mean age 41 (11.9); 99.1% female; 100% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 – 180 days after surgery	n	y
6	Bicket 2019	United States	Nationwide Insurance Claims Database: The IBM MarketScan® Research Databases which includes claims data across the continuum of care from large employers and healthcare plans (2010 – 2015)	Surgery (Mixed)	912,882	Mean age 44.5 (12.2); 56.5% female; 100% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 – 180 days after surgery**	y (we prioritized in the main analysis of risks the outcome that was prioritized in the study and used in risk factor analysis)	y
7	Brescia 2019	United States	Nationwide Insurance Claims Database: The Truven Health MarketScan Research Databases (2010 – 2014)	Surgery (Cardiothoracic)	3,026	Mean age 64 (11); 55.2% female; 100% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 - 180 days after surgery	n	y
8	Brummett 2017	United States	Nationwide Insurance Claims Database: Clinformatics Data Mart Database (2012 – 2015)	Surgery (Mixed)	36,177	Mean age 44.6 (11.9); 66.1% female; 100% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 - 180 days after surgery	n	y
9	Carroll 2012	United States	Prospective collection of data in a surgical clinical setting (2007 – 2009)	Surgery (Mixed)	109	Across surgical groups: Mean age ranged from 52 – 63y; % female ranged from 63 – 100; ~80% opioid-naive	Not achieving opioid cessation (5 consecutive days of no opioid use) by day 150 post-operatively.	n	y
10	Delgado 2018	United States	Nationwide Insurance Claims Database: Clinformatics Data Mart Database (2011 – 2015)	Injury, trauma, or ED presenting pain	25,849 (6,463 filled opioids at baseline)	For 6,463 who filled opioids at baseline (included SG): Median age 38 (28 – 52); 52.5% female; 100% opioid-naive	Received 1 or more opioids 30 – 180 days after index ED visit**	y (we prioritized in the main analysis of risks the outcome that was prioritized in the study and used in risk factor analysis)	y

11	Deyo 2016	United States	Oregon Prescription Drug Monitoring Program, Oregon vital records, and a statewide hospital discharge registry (2011 – 2014)	Mixed acute and chronic pain conditions including *Dental pain or procedures.*	536,767 (243,427 non-cancer non-chronic pain; 38,302 dental pain or procedures)	93.3% ≥ 18y; % female not reported; 100% opioid-naive	Six or more opioid fills during the 12 months following the index prescription fill	n	y, we included RF data on the non-cancer non-chronic pain subgroup
12	Finney 2019	United States	Nationwide Insurance Claims Database: The Truven Health MarketScan Research Databases (2009 – 2015)	Surgery (Orthopedics)	36,562	Mean age 48.6 (11.3); 88.1% female; 100% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 – 180 days after surgery	n	y
13	Friedman 2019	United States	Prospective collection of data following ED visits by telephone interview + medical records, including the New York State prescription monitoring program database (2017 – 2018)	Injury, trauma, or ED presenting pain	484	Mean age 46 (16); 56% female; 100% opioid-naive	Persistent opioid use defined as filling ≥ 6 prescriptions within the 6 month FU period**	y (in studies that did not conduct RF analysis or reported risk and RF analysis using multiple outcomes, we prioritized the most conservative outcome measuring use for the longest period and using continuous or frequent use measures in risk)	n (no RF analysis was conducted in the study)
14	Gil 2019	United States	Nationwide Insurance Claims Database: The Truven Health MarketScan Research Databases (2009 – 2015)	Surgery (Orthopedics)	104,154	Age distribution: 18 – 29 (9.4%), 30 – 39 (9%), 40 – 49 (21.4%), 50 – 59 (33%), 60 – 69 (21%), ≥ 70 (6.3%); 35.5% female; 100% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 - 180 days after surgery	n	y
15	Goesling 2016	United States	Secondary analysis of data from a prospective outcome study in a clinical surgical setting (2010 – 2013)	Surgery (Orthopedics)	574 (407 opioid-naive)	No prolonged use group mean age 63.5 (10.4); 51.3% female Prolonged use group mean age 62.6 (11.3) Overall 71% opioid-naive	Confirmation of opioid use by the patient 6 months postoperatively	n	y
16	Hadlandsmyth 2018	United States	Veterans' Health Administration Datasets which include data on inpatient care, outpatient care, and outpatient pharmacy services (2013 – 2015)	Surgery (Orthopedics)	6,653 (5322 opioid-naive)	Median age (66); 7% female; 80% opioid-naive	Continuous opioid use over 12 months (no lapses lasting > 14 days)**	y (we prioritized in the main analysis of risks the outcome that was prioritized in the study and used in risk factor analysis)	y, we included only RF data on opioid-naive SG

17	Halbert 2016	United States	National Survey: The Medical Expenditure Panel Surveys Household Component (MEPS-HC) (2005 – 2011)	Mixed acute and chronic pain conditions including *Injury, trauma, or ED presenting pain* and *Dental pain or procedures*.	33,450 (2160 Injury, trauma, or ED presenting pain; 796 Dental pain or procedures; 2995 overall acute pain starting opioids at baseline)	Mean age 48 (17); 54.4% female; 100% opioid-naive	Receiving 3 or more opioid prescriptions over ~ 15 months of follow up	n	y, we included only RF data on acute pain SG that started opioids at baseline
18	Hooten 2015	United States	Medical records + electronic prescription recording system in two clinical centres (2005 – 2010)	Mixed acute and chronic pain conditions including *Surgery (Mixed)*, and *Injury, trauma, or ED presenting pain*	293 (123 Surgery, 34 Injury, trauma, or ED presenting pain)	Age distribution: 0 - 18y (9.2%), 19 - 29y (14.3%), 30 - 49 (21.2%), 50 - 64 (22.9%), ≥65 (32.4%); 61% female; 100% opioid-naive	≥ 90 days' supply of opioids over 1 year	n	n (only 53.6% with acute pain (surgery or trauma) and no SG analysis of RF factors presented)
19	Jeffery 2018	United States	Nationwide Insurance Claims Database: Optum Labs Data Warehouse which includes data on health care service utilization and pharmacy claims (2009 – 2015)	Mixed acute and chronic pain including *Injury, trauma, or ED presenting pain*	5.2 million fills (682,343 for Injury, trauma, or ED presenting pain)	Based on type of insurance: Median age (IQR) and % female: Commercial 38 (25 - 51), 52.7%; Aged medicare 73 (68 - 79), 57.2%; Disabled medicare 57 (51-61), 51.2%. Overall: 100% opioid-naive	Long-term opioid use defined as > 10 fills or 120 days supplied in 1 year	n	n (< 20% in ED and no SG analysis of RF factors presented)
20	Johnson 2016	United States	Nationwide Insurance Claims Database: The Truven Health MarketScan Research Databases (2010 – 2012)	Surgery (Plastics)	59,725	Age distribution: 18 – 34y (7.5%), 35 – 44y (11.1%), 45 – 54y (27.2%), 55 – 64y (32.2%), ≥65y (22%); 60% female; 100% opioid-naive.	New persistent opioid use defined as filling at least one opioid prescription 90 - 180 days after surgery	n	y
21	Karhade 2019	United States	Electronic Medical Records in two academic medical centers and thee community hospitals (2000 – 2018)	Surgery (Spine)	2,737 (2,028 opioid-naive)	Median age 51 (44 - 59); 52.6% female, 74.1% opioid-naive.	Uninterrupted filling of prescription opioids extending to at least 90 - 180 days after surgery	n	y, RF data on entire cohort (74.1% opioid naive)
22	Kim 2017	United States	Nationwide Insurance Claims Database: Clinformatics Data Mart Database (2004 – 2013)	Surgery (Orthopedics)	57,545 (7,425 opioid-naive)	Entire sample: Mean age 61.5 (7.8); 57% female; 12.9% opioid-naive.	Persistent opioid use, definition derived from trajectory models of opioid use in 12 months of follow up	n	y, we included only RF data on opioid-naive SG
23	Lee 2017	United States	Nationwide Insurance Claims Database: The Truven Health MarketScan Research Databases (2010 – 2014)	Surgery (Mixed)	68,463 (39,877 opioid-naive)	Opioid-naive group: (a) No prolonged use: Mean age 58.9 (12.7), 76.6% female (b) Prolonged use: Mean age 58.3 (12.4), 78.2% female Overall: 58% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 - 180 days after surgery	n	y, we included only RF data on opioid-naive SG

24	Marcusa 2017	United States	Nationwide Insurance Claims Database: The Truven Health MarketScan Research Databases (2009 – 2015)	Surgery (Plastics)	4,113 (3,691 filled an opioid prescription at baseline)	Age distribution: 18–34 (4%), 35–44 (23%), 45–54 (38%), 55–64 (29%), ≥ 65 (6%); 100% female; 100% opioid-naive	New persistent opioid use defined as filling at least one opioid prescription 90 - 120 days after surgery	n	y
25	Meisel 2019	United States	Washington State Insurance Claims Data for Medicaid Enrollees + Prescription Drug Monitoring Program Data (2013 – 2015)	Injury, trauma, or ED presenting pain	23,381	Mean age 32; 57.6% female; 100% opioid-naive	≥ 1 opioid prescription in every calendar quarter over 12 months**	y (in studies that did not conduct RF analysis or reported risk and RF analysis using multiple outcomes, we prioritized the most conservative outcome measuring use for the longest period and using continuous or frequent use measures in risk)	n (the outcome in RF analysis is a composite outcome including measures of prolonged use + high-risk prescribing)
26	Musich 2019	United States	Nationwide Insurance Claims Database: United-Healthcare (2016 – 2017)	Mixed acute and chronic pain including *Surgery (Orthopedic)*, and *Injury, trauma, or ED presenting pain*	180,498 (16,892 Surgery, 5,010 Injury, trauma, or ED presenting pain)	Age distribution: 65-69 (24.6%), 70-74 (28.7%), 75-79 (20.6%), 80-85 (12.3%), ≥ 85 (12.8%); 60.9% female; 100% opioid-naive	Chronic opioid use was defined as ≥ 2 prescriptions and >90 days' supply of opioids over 1 year	n	n (mixed acute and chronic pain population with only: 5% new back pain, 3% TKA, 4% trauma, and no SG analysis for RF factors)
27	Noureldin 2019	United States	Nationwide Insurance Claims Database: The Truven Health MarketScan Research Databases (2009 – 2015)	Other (Inflammatory bowel disease flare)	15,119 (5,411 opioid-naive)	Opioid-naive group: Mean age 43.9 (15.8); 54.3% female; 35.8% opioid-naive	Persistent opioid use defined as at least 1 additional opioid fill 90 – 365 days from initial prescription	n	y, we included only RF data on opioid-naive SG
28	Roughead 2019	Australia	VA Administrative Health Claims Database which contains data on all prescription medicines, medical, and allied health services, and hospitalisations for veterans and their dependants (2014 – 2015)	Surgery (Mixed)	3,907	Median Age 71 (66-84); 31% female; 100% opioid-naive	Continuous use until ≥ 90 days from discharge. Cessation was defined as a period without an opioid prescription that was equivalent to three times the estimated supply duration.	n	n (no RF analysis was conducted in the study)
29	Schroeder 2019	United States	Nationwide Insurance Claims Database: Optum Research Database which includes data on inpatient and outpatient service use and pharmaceutical claims (2015)	Dental pain or procedures	14,888	Mean age 21.8 (2.4); 52.9% female; 100% opioid-naive	At least 1 additional filled opioid prescription at 90 to 365 days after the initial prescription	n	y

30	Shah 2017	United States	Nationwide Insurance Claims Database: Intercontinental Marketing Services Lifelink1 Database which includes inpatient, outpatient, and pharmacy claims data (2006 – 2015)	Mixed acute and chronic pain including *Surgery (Mixed)*, *Injury, trauma, or ED presenting pain*, and *Dental Pain or Procedures*	1,353,902 (179,482 Surgery; 192,349 Injury, trauma, or ED presenting pain; 22,929 Dental Pain or Procedures; 810,035 'no chronic pain condition diagnosis in 6 months before index prescription')	By prolonged use: (a) No Prolonged opioid use: 18 – 64 (87.9%); 53.67% female (b) Prolonged opioid use: 18 – 64 (88.2%); 55.98% female Overall: 100% opioid-naive	Continuous use ≥ 365 days from index prescription. Opioid discontinuation was defined as at least 180 continuous days without opioid use from the end date of the last opioid prescription. The date of discontinuation was defined as the end date of the last opioid prescription before 180 opioid-free days.	n	y, we included RF data only for the group with 'no chronic pain condition diagnosis in 6 months before index prescription'
31	Shoenfeld 2017	United States	Nationwide Insurance Claims Database: Military Health System Data Repository (MDR) for patients receiving surgical care through TRICARE insurance, which includes data on healthcare use and pharmacy claims (2006 – 2014)	Surgery (Spine)	9,991 (8,388 filled opioids at baseline)	Mean age 46.4 (11); 37% female; 100% opioid-naive	Continuous opioid use over 12 months from day of surgery (no lapses lasting > 30 days)**	y (in studies that reported the same outcome measured at multiple time points and a time-to-event analysis, we prioritized use at or closest to 12 months)	y, RF analysis was conducted on 8,388 who filled opioids at baseline only, which we included
32	Smith 2019	United States	Electronic Medical Records at one healthcare centre (2011 – 2017)	Other (Curative intent radiation therapy for head and neck malignancies)	311	Mean age 58.4 (12.2); 21.9% female; 100% opioid-naive	Any use at or beyond 180 days from completion of radiation therapy.	n	y
33	Swenson 2018	United States	Nationwide Insurance Claims Database: Optum Clinformatics Data Mart Database (2011 – 2014)	Surgery (Obstetrics and Gynecology)	24,331	Age distribution by prolonged use: (c) No Prolonged opioid use: <40 (18.3%), 40 – 44 (25.3%), 45 – 49 (27.7%), ≥ 50 (28.8%) (d) Prolonged opioid use: <40 (17.2%), 40 – 44 (16.4%), 45 – 49 (24.6%), ≥ 50 (41.8%) Overall 100% female; 100% opioid-naive.	New persistent opioid use defined as ≥ 39 days supplied and ≥ 2 opioid fills, with at least 1 fill each during the 15 – 90 day and the 91 – 180 day postoperative periods	n	y

34	Thiels 2019	United States	Nationwide Insurance Claims Database: Optum Labs Data Warehouse (2009 – 2018)	Surgery (Mixed)	444,764[#]	Age not reported; % female; 100% opioid-naive	An opioid use episode starting in the 180 days after surgery that spans at least 90 days and includes either ≥ 10 opioid fills or ≥ 120 days' supply of opioids (CONSORT definition)**	y (in studies that did not conduct RF analysis or reported risk and RF analysis using multiple outcomes, we prioritized the most conservative outcome measuring use for the longest period and using continuous or frequent use measures in risk and RF analysis)	y
35	Wu 2019	United States	Medical records: Community-based. Integrated healthcare system records (2008 – 2015)	Other (Acute pancreatitis)	4,307 (4,021 with complete outcome data)	Median age 57.4 (44 - 70.2); 52% female; 100% opioid-naive	Persistent opioid use was defined as opioid dispensation at discharge or within the first 2 weeks after discharge and again within 90 to 180 days from the discharge date of the index hospitalization.	n	y, we included RF data for SG analyzed in study (with complete outcome data)

RF Risk factor SG Subgroup; ED Emergency Department; FU Follow Up; TKA Total Knee Arthroplasty
*Categories: (1) Surgery; (2) Injury, trauma, or ED presenting pain;(3) Dental pain or procedures; (4) Mixed; (5) Other
**We only report the definition of the outcome included in the review when multiple outcome definitions are used in a study.
[#] 357,884 filled opioids at baseline (~ 80%), but no SG data

Appendix 2-F: Summary of assessment of risk of bias in included studies.

	Risks ROB, Iorio et al. criteria* (n=35)				Risk factor measures of association ROB, QUIPS tool by Hayden et al. (n=29)						
Study First Author (Year)	Study participation	Study attrition	Outcome measurement	OVERALL RISK OF BIAS	Study participation	Study attrition	Risk factor measurement**	Outcome measurement	Study confounding***	Statistical analysis and reporting	OVERALL RISK OF BIAS
AlDabbagh 2014	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	High
AlDabbagh 2016	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	High
Basilico 2019	Low	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Bateman 2016	Low	Low	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Low	Moderate
Bennett 2018	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Bicket 2019	Low	Low	Low	Low	Low	Low	Moderate	Low	Low	Low	Moderate
Brescia 2019	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate	Moderate
Brummett 2017	Low	Low	Low	Low	Low	Low	Moderate	Low	Low	Low	Moderate
Carroll 2012	High	High	Moderate	High	High	High	Low	Moderate	High	Moderate	High
Delgado 2018	Low	Low	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Low	Moderate
Deyo 2016	Moderate	Moderate	Low	Moderate	Low	Moderate	Low	Low	High	Low	High
Finney 2019	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Friedman 2019	High	Low	Low	Low	NA	NA	NA	NA	NA	NA	NA
Gil 2019	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Goesling 2016	High	Moderate	High	High	High	Moderate	Low	High	High	High	High
Hadlandsmyth 2018	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Halbert 2016	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	High	Low	High
Hooten 2015	Moderate	Moderate	Moderate	Moderate	NA	NA	NA	NA	NA	NA	NA
Jeffery 2018	Low	Low	Low	Low	NA	NA	NA	NA	NA	NA	NA
Johnson 2016	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Karhade 2019	Low	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Kim 2017	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	High	High
Lee 2017	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Marcusa 2017	Low	Low	Low	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate
Meisel 2019	Low	Moderate	Low	Moderate	NA	NA	NA	NA	NA	NA	NA
Musich 2019	Low	Low	Low	Low	NA	NA	NA	NA	NA	NA	NA
Nuoreldin 2019	Low	Low	Low	Low	Low	Low	Moderate	Low	High	Moderate	High

Roughead 2019	Low	Low	Low	**Low**	NA	NA	NA	NA	NA	NA	NA
Schroeder 2019	Low	Low	Low	**Low**	Low	Low	Moderate	Low	High	Low	**High**
Shah 2017	Moderate	Moderate	Low	**Moderate**	Low	Moderate	Low	Low	Low	Low	**Moderate**
Shoenfeld 2017	Low	Low	Low	**Low**	Low	Low	Moderate	Low	Moderate	Low	**Moderate**
Smith 2019	Moderate	Moderate	High	**High**	Moderate	Moderate	Moderate	High	High	High	**High**
Swenson 2018	Low	Low	Low	**Low**	Low	Low	Moderate	Low	High	Moderate	**High**
Thiels 2019	Low	Low	Low	**Low**	Low	Low	Moderate	Low	Low	Low	**Moderate**
Wu 2019	Low	Low	Low	**Low**	Low	Low	Moderate	Low	Moderate	Low	**Moderate**

ROB risk of bias; RF risk factors; QUIPS QUality In Prognosis Studies tool. **Overall risk of bias:** High, Moderate, Low, N/A

*Criteria: (1) Was there a representative and well-defined sample of patients?; (2) Was follow-up sufficiently long and complete?; and (3) Were objective and unbiased outcome criteria used?

** in GRADE assessment of study limitations for each risk factor, this domain was taken into consideration. We rated the following factors to be at low ROB in risk factor measurement in every included study: age, sex, race (Black, Asian, and Hispanic), average daily dose of first-prescription, days' supply of first-prescription, opioid type of first-prescription, total perioperative MME, and pre-operative opioid fill. We rated all other factors to be at moderate risk of bias in this domain.

*** in GRADE assessment of study limitations for each risk factor, this domain was taken into consideration. For risk factors for which sensitivity analysis based on adjustment quality was possible, we took the results of the sensitivity analysis into account when making a judgement. When the results did not change when only the studies with ideal adjustment were included, we considered the domain to be low risk of bias, even if risk of confounding was determined to be moderate or high, and this was taken into account in the assessment of study limitations overall.

Appendix 2-G: Study measure of association, sample size analyzed, and review risk factors reported.[1]

Study	Measure of association	Sample size analyzed	Review Risk factors Reported in Study (Point estimates and 95% CI listed if not included in meta-analysis)[2]
AlDabbagh 2014	HR*	639	Age categorical (HR 1.5, 95% CI 1.3 – 1.9) for > 50y vs. below ; Sex (HR 1.1, 95% CI 0.9 - 1.4)
AlDabbagh 2016	HR*	891	Age categorical (HR 1.9, 95% CI 1.5 – 2.3) for ≥ 70y vs. below ; Sex (HR 1.2, 95% CI 1.0 - 1.4)
Basilico 2019	Coeff.	17,961	Sex (Coeff. -0.07, SE 0.04) for male vs. female; Comorbidity continuous (Coeff. -0.06, SE 0.02); Tramadol vs. other short acting (Coeff. 0.195, SE 0.17); Long-acting opioid (morphine) vs. other short acting (Coeff. 0.521, SE 0.319)
Bateman 2016	OR	80,127	Age categorical (OR 0.54, 95% CI 0.43 – 0.63) for ≥ 40 y vs. 20-29 y; Depression; Psychosis; Tobacco use; Drug use; Average daily dose MME of index prescription(OR 1.3, 95% CI 0.87 – 1.93) for 112.5 MME vs. <81 MME; Days' supply of index prescription OR (1.86, 95% CI 0.81 – 4.3) for ≥ 8 days vs. ≤ 3 days.
Bennett 2018	OR	11,257	Age categorical; Sex; Education; Income; Comorbidity continuous; Back pain; Arthritis; Neck pain; Anxiety; Depression; Psychosis; Total periop. MME
Bicket 2019	OR	912,882	Age categorical; Sex; Comorbidity continuous; Back pain; Arthritis; Neck pain; Anxiety; Depression; Tobacco use; Alcohol use; Drug use; Preop. fill; Total periop MME
Brescia 2019	OR	3,026	Age categorical (OR 0.78, 95% CI 0.62 – 0.95) for > 64y vs. ≥ 64 y; Sex
Brummett 2017	OR	36,177	Age categorical; Sex; Race Black; Race Asian; Race Hispanic; Education; Comorbidity continuous; Back pain; Arthritis; Neck pain; Anxiety; Depression; Tobacco use; Alcohol use; Drug use; Preop. fill; Total periop. MME
Carroll 2012	HR*	109	Age continuous (unadj. HR 1.08, 95% CI 0.81 – 1.43); sex unadj. HR 1.01 (0.58 - 1.69); anxiety (unajd. HR 0.69 (0.52 - 0.93)); depression (HR 0.62 (0.46 - 0.83); tobacco HR 0.77 (0.48 - 1.24); alcohol HR 1.2 (0.71 - 1.5); marijuana (unadj. HR 0.56, (0.20 – 1.54)
Delgado 2018	OR	6,463	Age categorical; sex; race Black; race Asian; race Hispanic; education; comorbidity continuous; depression; psychosis; drug; days' supply of first-prescription
Deyo 2016	OR	536,767	Number of prescriptions filled and total MME over entire initiation month
Finney 2019	OR	36,562	Age categorical; sex; income; comorbidity categorical; back pain; arthritis; neck pain; anxiety; depression; drug use; preoperative fill; total periop. MME
Gil 2019	OR	104,154	Age categorical; sex; income; comorbidity continuous; back pain; arthritis; neck pain; anxiety; depression; psychosis; alcohol use; drug use; preoperative fill; total periop. MME
Goesling 2016	OR	407	Age continuous; sex
Hadlandsmyth 2018	RR	5,322	Age categorical RR 0.77 (0.49 – 1.20); sex RR 0.53 (0.21 - 1.35); comorbidity categorical RR 0.69 (043 - 1.14) 2/3 vs. 0/1; back pain RR 1.25 (0.84 - 1.86); arthritis RR 1.25 (0.84 - 1.86); anxiety RR 1.04 (0.63 - 1.71); depression RR 0.93 (0.56 - 1.54); psychosis RR 1.04 (0.63 - 1.71); drug RR 1.74 (1.01 - 2.99)
Halbert 2016	OR	2,995	Depression
Johnson 2016	OR	59,725	Age categorical; sex; income; comorbidity categorical; back pain; arthritis; neck pain; depression; tobacco use; alcohol use; drug use
Karhade 2019	OR	2,737	Depression (identified as an important predictor), tobacco use(identified as an important predictor)
Kim 2017	OR	7,425	Comorbidity continuous
Lee 2017	OR	39,877	Age continuous; sex; income; comorbidity continuous; anxiety; depression; drug use; preoperative fill
Marcusa 2017	OR	4,113	Age categorical; income; comorbidity categorical; anxiety; depression; psychosis; drug use
Noureldin 2019	HR	5,411	Anxiety HR 1.12 (1.0 - 1.26); depression HR 1.29 (1.13 - 1.47); drug use HR 1.36 (1.2 - 1.54)
Schroeder 2019	OR	14,888	Sex; race Black; race Asian; race Hispanic; drug use
Shah 2017	HR*	810,035	Average DD MME of first-prescription HR 0.96 (0.95 – 0.97) ≥ 90 MME compared to 0-24 MME; days supply of first-prescription HR 0.68 (0.67 – 0.68) 3-4 d vs. 1-2 d; tramadol vs. other short-acting opioids HR 0.95 (0.95 – 0.95); long- vs. short-acting opioids HR 0.76 (0.73 – 0.79)
Shoenfeld 2017	HR*	8,388	Age categorical HR 1.01 (0.88 – 1.16); sex HR 1.01 (0.97 - 1.1); income HR 1.06 (1.01 - 1.12); comorbidity categorical HR 1.06 (0.94 - 1.20) ≥2 vs. 0; anxiety HR 0.85 (0.67 - 1.06)
Smith 2019	OR	311	Age continuous unadjusted OR 1 (0.99 - 1.01); sex unadjusted OR 0.59 (0.22 - 1.33); tobacco unadjusted OR 2.94 (1.16 - 7.46); alcohol use (adjusted and presented in forest plot)
Swenson 2018	OR	24,331	Age continuous; race Black; race Asian; race Hispanic; back pain; neck pain; depression; pre-operative fill
Thiels 2019	OR	444,764	Age categorical; sex; race Black; race Asian; race Hispanic; arthritis; depression; psychosis; alcohol use; drug use; tramadol vs. other short-acting opioids OR 1.41 (1.08 – 1.75); long-acting opioid vs. short-acting opioids OR 1.69, 95% CI 1.36 – 2.02
Wu 2019	OR	4,021	Age categorical; sex; race Black; race Asian; race Hispanic; comorbidity categorical; tobacco use; alcohol use

[1] Some of the included studies reported factors that were not identified a-priori and were not reported consistently across studies – those factors are not included in the review, and therefore not listed in this table.

[2] **For all other estimates refer to forest plots in the Appendix)**

HR Hazards Ratio; Coeff. Coefficient; OR Odds Ratio; RR Risk Ratio; H High; M Moderate; Periop. Perioperative; DD Daily Dose

*Outcome is time to opioid cessation; point estimate > 1 means higher risk of stopping opioids, and < 1 lower risk of stopping (comparable to higher risk of prolonged use)

Appendix 2-H: GRADE domains and the overall certainty in the evidence on the associations between the included risk factors and prolonged opioid use. Table adapted from Huguet et. al. [17]

	Overall	Included in narrative analysis				Included in meta-analysis		GRADE domains							
Risk factor	No. studies	No. studies	+	0	-	No. studies (No. subjects)	Effect size (OR, 95% CI)	Study Design	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/Large effect size	Dose effect	Overall Certainty
Age (continuous, years)	5, 9	2	0	2	0	3, 7 (64,615)	1 (0.99 – 1.01)	Ideal	Very serious	No	No	No	No	No	NA	+++ Due to study limitations
Age (categorical, ≥ 60 y vs. 18-34y)	16	6	0	3	3	10 (1,620,118)	1.08 (0.89 – 1.30)	Ideal	No* (All studies in quant. analysis at RF-specific low overall ROB.)	Yes	No	No	No	No	NA	+++ Due to inconsistency
Sex (Female vs. male)	20	7	0	6	1	13, 17 (1,674,203)	1.06 (1.00 – 1.13)	Ideal	Serious	Yes	No	No	Yes	No	NA	++ Due to study limitations, due to inconsistency, due to potential publication bias
Race (Black)	6	0	0	0	0	6 (530,644)	1.24 (1.19 – 1.29)	Ideal	No*	No	No	No	No	No	NA	++++
Race (Asian)	6	0	0	0	0	6 (530,644)	0.79 (0.72 – 0.86)	Ideal	No*	No	No	No	No	No	NA	++++
Race (Hispanic)	6	0	0	0	0	6 (530,644)	0.98 (0.94 – 1.03)	Ideal	No*	No	No	No	No	No	NA	++++

Education (HS vs. college degree)	3	0	0	0	0	3 (53,897)	1.23 (1.02 – 1.48)	Ideal	Serious	No	No	No	Yes	No	NA	++ Due to study limitations, due to potential publication bias
Income (MHI < 40K vs. ≥ 70K)	7	1	0	0	1	6, 7 (255,688)	1.21 (0.91 – 1.60)	Ideal	Serious	No	No	Yes	No	No	No	++ Due to study limitations, due to imprecision
Comorbidity (continuous, no.)	7, 11	0	0	0	0	7, 11 (1,118,235)	1.07 (1.03 – 1.11)	Ideal	No*	No	No	No	No	No	NA	++++
Comorbidity (>3 vs. 0 count)	4	0	0	0	0	4 (104,421)	1.53 (1.05 – 2.24)	Ideal	Serious	Yes	No	No	No	No	Unclear	++ Due to study limitations, due to inconsistency
Back pain	9	1	0	1	0	8 (1,265,215)	1.25 (1.14 – 1.36)	Ideal	No*	No	No	No	Yes	No	NA	+++ Due to potential publication bias
Arthritis	9	1	0	1	0	8 (1,610,931)	1.22 (1.12 – 1.32)	Ideal	No*	No	No	No	No	No	NA	++++
Neck pain	7	0	0	0	0	7 (1,185,088)	1.12 (1.06 – 1.17)	Ideal	No*	No	No	No	Yes	No	NA	+++ Due to potential publication bias
Anxiety	11, 15	4	2	2	0	7, 11 (1,145,022)	1.22 (1.15 – 1.30)	Ideal	No*	No	No	No	No	No	NA	++++

Depression	17, 20	3	4	1	0	13, 17 (1,763,427)	1.41 (1.28 – 1.56)	Ideal	No* (Excluding high ROB - slightly attenuated; excluding less than ideal - slightly strengthened)	No	No	No	No	No	NA	++++
Psychosis	7	1	0	1	0	6 (650,878)	1.11 (0.82 – 1.50)	Ideal	Serious	No	No	Yes	Yes	No	NA	++ Due to study limitations, due to imprecision, due to potential publication bias
Tobacco	8	3	2	1	0	5 (1,092,932)	1.47 (1.24 – 1.75)	Ideal	No*	No	No	No	Yes	No	NA	+++ Due to potential publication bias
Alcohol	8	1	0	1	0	7 (1,562,034)	1.38 (1.20 – 1.59)	Ideal	No*	No	No	No	Yes	No	NA	+++ Due to potential publication bias
Drugs	13, 17	2	2	0	0	11, 15 (1,739,732)	1.55 (1.31 – 1.83)	Ideal	No*	No	No	No	No	No	NA	++++
Marijuana	2	2	0	2	0	0	-	Ideal	Very serious	No	No	Yes	Yes	No	NA	+ Due to study limitations, due to imprecision, due to potential publication bias
Average DD of first prescription	2	2	1	1	0	0	-	Ideal	No	Yes	No	Yes	Yes	No	No	+ Due to study limitations, due to inconsistency, due to imprecision, due to potential publication bias
Total MME of first-prescription	3	3	3	0	0	0	-	Ideal	Serious	No	No	Yes	Yes	No	Yes	+ Due to study limitations, due to imprecision, due to potential publication bias

Days' supply of first prescription	3	3	1	2	0	0	'	Ideal	No	No	No	Yes	Yes	No (vote)	Yes (vote)	++ Due to imprecision, due to potential publication bias
Opioid type of first prescription (Long- vs. short-acting)	3	3	2	1	0	0	'	Ideal	No	No	No	No	Yes	No	NA	+++ Due to potential publication bias
Opioid type of first prescription (Tramadol vs. other)	3	3	2	1	0	0	'	Ideal	No	No	No	No	Yes	No	NA	+++ Due to potential publication bias
Total perioperative MME	5	0	0	0	0	5 (1,101,032)	1.36 (0.96 – 1.92)	Serious (Due to data-driven and inconsistent MME cut-off points)	No	No	No	No	No	No	Unclear	+++ Due to study limitations
Preoperative opioid fill	6, 10	0	0	0	0	6, 10 (1,153,983)	1.49 (1.27 – 1.73)	Ideal	Serious	Yes	No	No	Yes	No	NA	+ Due to study limitations, due to inconsistency, due to potential publication bias

* Excluding high ROB and less than ideal adjustment in sensitivity analysis showed similar results

Overall certainty: + very low; ++ low; +++ moderate; ++++ high

+ = number of studies (or cohorts) that found a higher risk of outcome in the presence of the risk factor (taking point estimate and 95% CI into account), 0 = number of studies (or cohorts) that found no association between the risk factor and outcome (taking point estimate and 95% CI into account) - = number of studies (or cohorts) that found a lower risk of outcome in the presence of the risk factor (taking point estimate and 95% CI into account)

GRADE (Hayden et al.): Start at high certainty with ideal risk factor study designs, which are observational study designs (cohort studies, registries, or database linkage studies) Foroutan 2020

Downgrade if: (1) **Study limitations:** Serious limitations when most evidence is from studies with moderate or unclear risk of bias for most bias domains; very serious limitations when most evidence is from studies with high risk of bias for almost all bias domains, (2) **Inconsistency:** Unexplained heterogeneity or variability in results across studies with differences of results not clinically meaningful; for meta-analysis: significant heterogeneity detected by test of heterogeneity and large I^2 value; for narrative summary: variations in effect estimates across studies with points of effect on either side of the line of no effect, and confidence intervals showing minimal overlap, (3) **Indirectness:** The study sample, the risk factor, and/or the outcome in the primary studies do not accurately reflect the review question, (4) **Imprecision:** For meta-analysis: (a) insufficient sample size and (b) no precise estimate of the effect size in the meta-analysis: confidence interval is excessively wide and overlaps the value of no effect and contain values implying that the factor plays an important role in protecting or putting the individual at risk; For narrative summary: Within-study imprecision, (a) sample size justification is not provided and there are less than 10 outcome events for each prognostic variable (for dichotomous outcomes) OR there are less than 100 cases reaching endpoint (for continuous outcomes); and (b) no precision in the estimation of the effect size within each primary study; across study imprecision: there are few studies and small number of participants across studies, (5) **Publication bias:** We recommend downgrading unless the value of the risk/protective factor in predicting the outcome has been repetitively investigated, ideally by phase 2 and 3. To assess for publication bias, we inspected funnels plots for asymmetry, used Egger's test to assess for small-study effects, and considered whether most or all studies included multiple risk factors that were assessed at the same time (which is likely to decrease publication bias).

Upgrade if: (1) **Moderate or large effect:** For meta-analysis: pooled effect is moderate or large; for narrative summary: moderate or large similar effect is reported by most studies, (2) **Exposure-gradient response:** For meta-analysis: gradient is present between analyses for factors measured at different doses; for narrative summary: possible gradient exists within and between primary studies. No: no concern, Some: some concern, Serious: serious concern. Y: yes, N: no, NA: not applicable, unclear: insufficient information available to rate item.

Appendix 2-I: Overall certainty in the evidence on the risk of prolonged opioid use. Table adapted from Huguet et. al. [17]

	Overall	Included in meta-analysis		GRADE domains								
Acute pain group	Number of participants (No. Studies)	Number of participants (No. Studies)	Event estimate size (risk, 95% CI)	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Moderate/Large effect size	Dose effect	Overall Quality	Notes
Surgery overall	25 with 26 groups*	(2,037,051)	6 (4 – 9)	No	Yes	No	No	Yes	No	Yes	+++ Due to inconsistency	Excluding studies at overall high ROB showed same results
Injury, trauma, or ED-presenting pain overall	11 with 12 groups*	(1,256,023)	9 (6 – 12)	No	Yes	No	No	Yes	No	Yes	+++ Due to study limitations, due to inconsistency, due to potential publication bias	Excluding studies at overall high ROB showed same results
Dental	4	(76,915)	3 (2 – 6)	Serious	No	No	No	No	No	Unclear	++++	

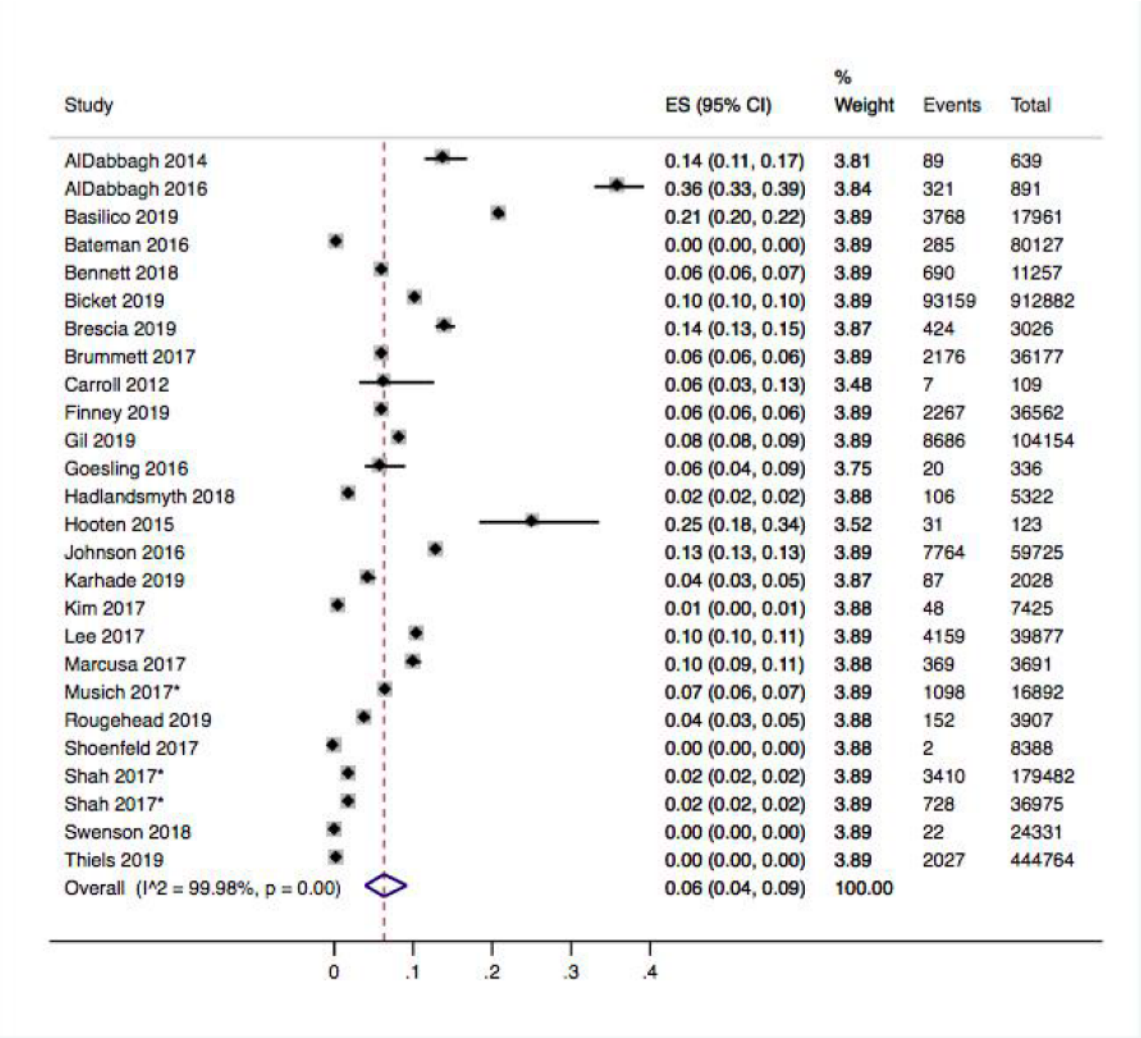
Overall certainty: + very low; ++ low; +++ moderate; ++++ high
GRADE: Start at HIGH with Longitudinal cohort studies and at MODERATE with large, simple, pragmatic trials with broad eligibility criteria that enrolled typical patients receiving opioids for acute pain. ***Downgrade if: (1)*** **Study limitations:** Serious limitations when most evidence is from studies with moderate or unclear risk of bias for most bias domains; Very serious limitations when most evidence is from studies with high risk of bias for almost all bias domains; *Except (i.e. do not downgrade)* if studies with moderate or high risk of bias contributed only a small proportion of the events to the pooled event rate OR if results are the same in studies with low and high risk of bias.; Note: if sensitivity analysis shows differences in estimates between studies with higher and lower risk of bias, use estimates from lower risk of bias studies and don't rate down confidence for risk of bias; (2) **Inconsistency:** Variability in estimates in general and specifically in relation to important decision thresholds (variation that would lead to alternative management approaches); Confidence intervals show minimal overlap; Note: I^2 can be misleading and should not be considered in the context of prognostic studies with large sample sizes of individual studies resulting in very narrow confidence intervals; Note: If inconsistency is observed but subgroup analyses show differences across categories and meet criteria for credibility (small number of hypotheses, a priori direction of observed rates, and consistent biological rationale) (ref 25 in Iorio) then use separate estimate for subgroups to resolve inconsistency; (3) **Indirectness:** Studies population does not correspond to population of interest; Measured outcome does not capture construct of interest; Note: consider range of decision makers who will be using review data; (4) **Imprecision:** Effect on patient or clinical decision would differ depending on whether the upper or lower boundary of the confidence interval represented the truth; (5) **Publication bias:** Tests based on ranking (e.g. Begg's test) show possible publication bias. ***Upgrade if: (1)*** **Moderate or large effect:** For meta-analysis: pooled effect is large; (2) **An increase in events over time:** Prolonged opioid use *decreases* over time following a well-defined pattern (linear or otherwise).

Appendix 2-J: Results of the association between total MME of first-prescription and prolonged opioid use in included studies. (n= 4)

Study	Measure	Categories	Adjusted OR (95%CI)
Delgado 2018	Total MME of first prescription	1–75	**Ref**
		76–150	1.33 (0.82–2.15)
		151–225	1.55 (0.65–3.73)
		≥ 226	4.15 (1.85–9.3)
Thiels 2019	Total MME of first prescription	1-199	**Ref**
		200 - 299	1.064 (0.903 - 1.255)
		300 - 399	1.304 (1.101 - 1.544)
		400 - 499	1.32 (1.088 - 1.603)
		500+	1.588 (1.309 - 1.926)
Wu 2019	Total MME of first prescription	Continuous	1.02 (1.00 – 1.04)
Deyo 2016	Total MME over entire initiation month	1–119	**Ref**
		120 - 279	1.42 (1.37 - 1.49)
		280 - 399	2.22 (2.10 - 2.34)
		400 - 799	2.96 (2.81 - 3.11)
		800 - 1599	4.63 (4.37 - 4.92)
		1600 - 2399	6.78 (6.21 - 7.40)
		2400 - 3199	11.27 (10.04 - 12.65)
		3200 - 3999	16.3 (13.71 - 19.37)

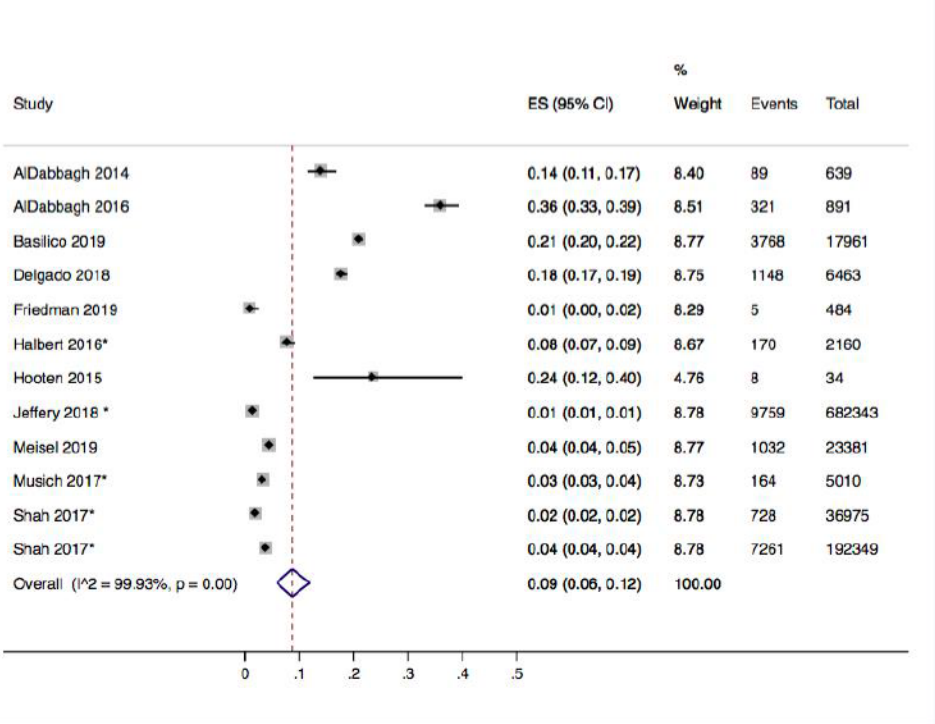
Appendix 2-K Figures

2-K-1: Study-specific and pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients receiving new opioids after surgery (random effects meta-analysis).

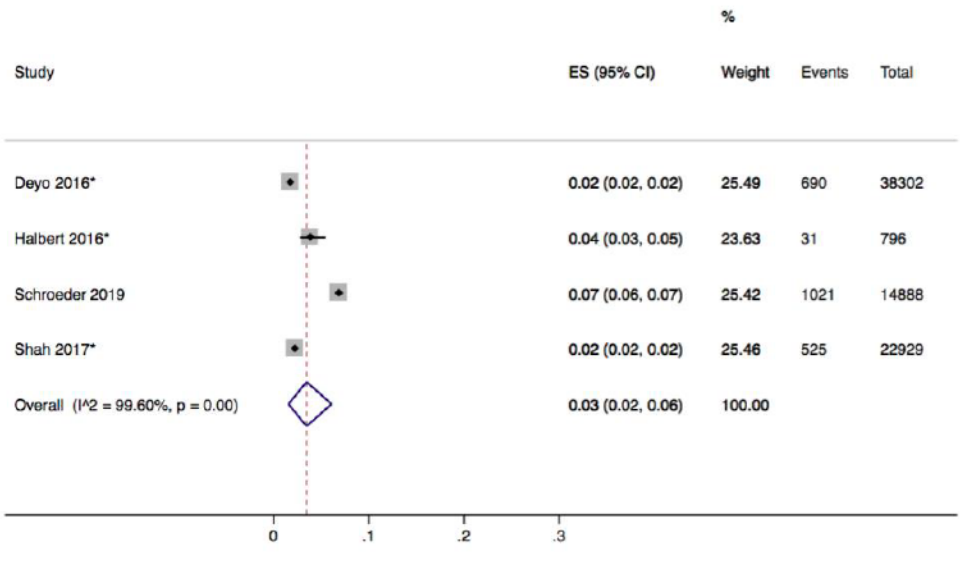


Bateman 2016, 0.36%; Shoenfeld 2017, 0.1%; Swenson 2018, 0.5%; Thiels 0.45%

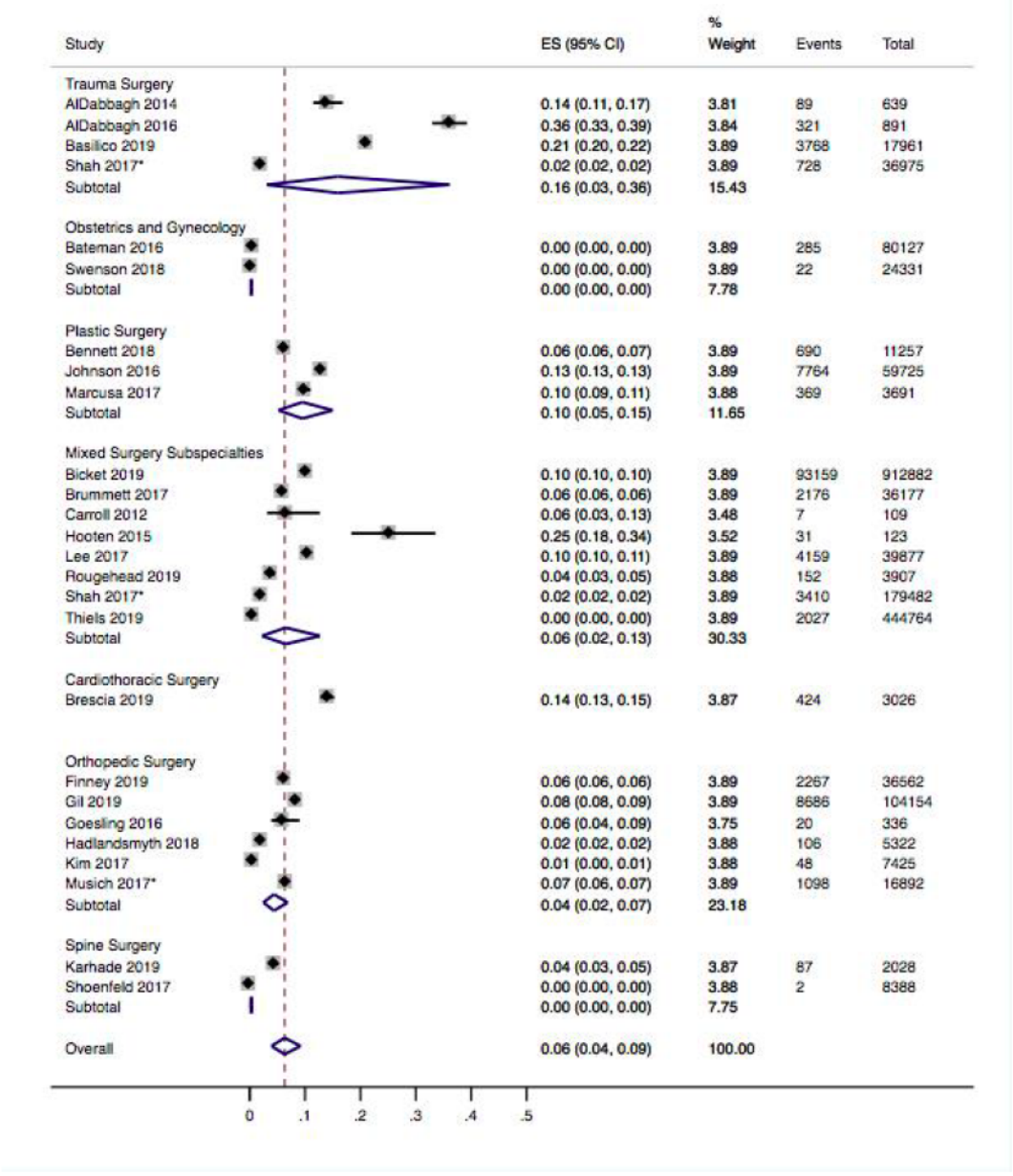
2-K-2: Study-specific and pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients receiving new opioids after injury, trauma, or emergency department presenting pain (random effects meta-analysis).



2-K-3: Study-specific and pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients receiving new opioids after dental pain or procedures (random effects meta-analysis).

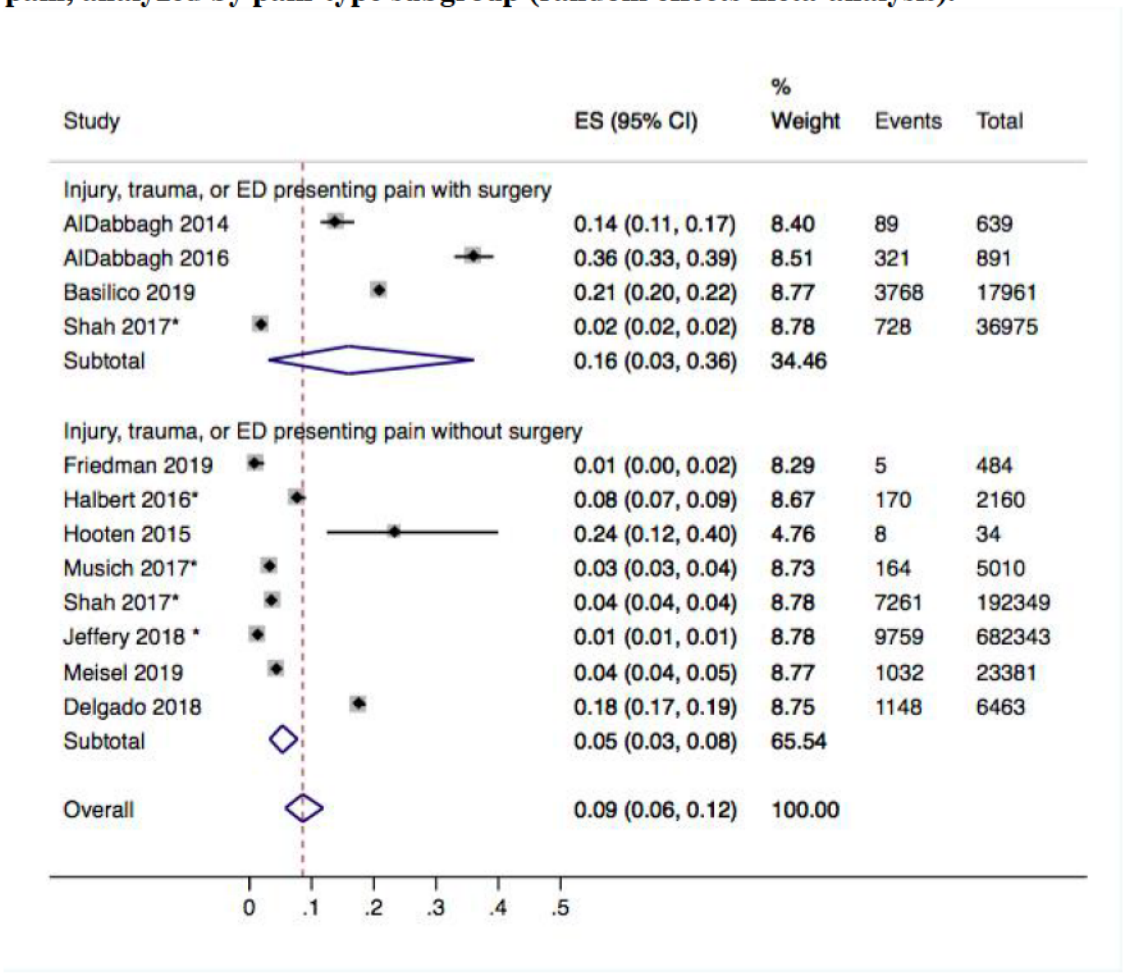


2-K-4: Study-specific and pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients receiving new opioids after surgery, analyzed by surgery subspecialty subgroup (random effects meta-analysis).

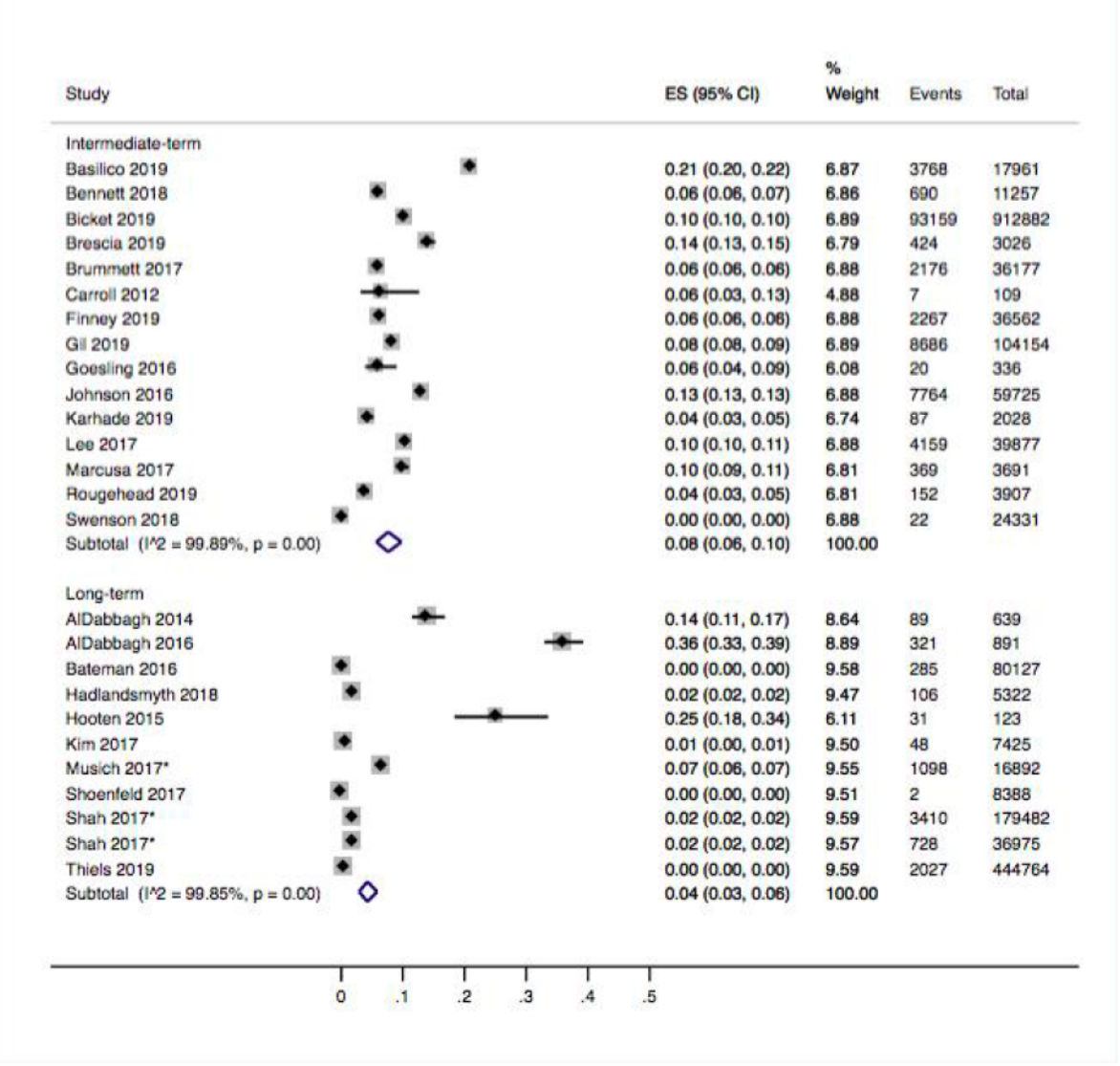


Bateman 2016, 0.36%; Shoenfeld 2017, 0.1%; Swenson 2018, 0.5%; Thiels 0.45%

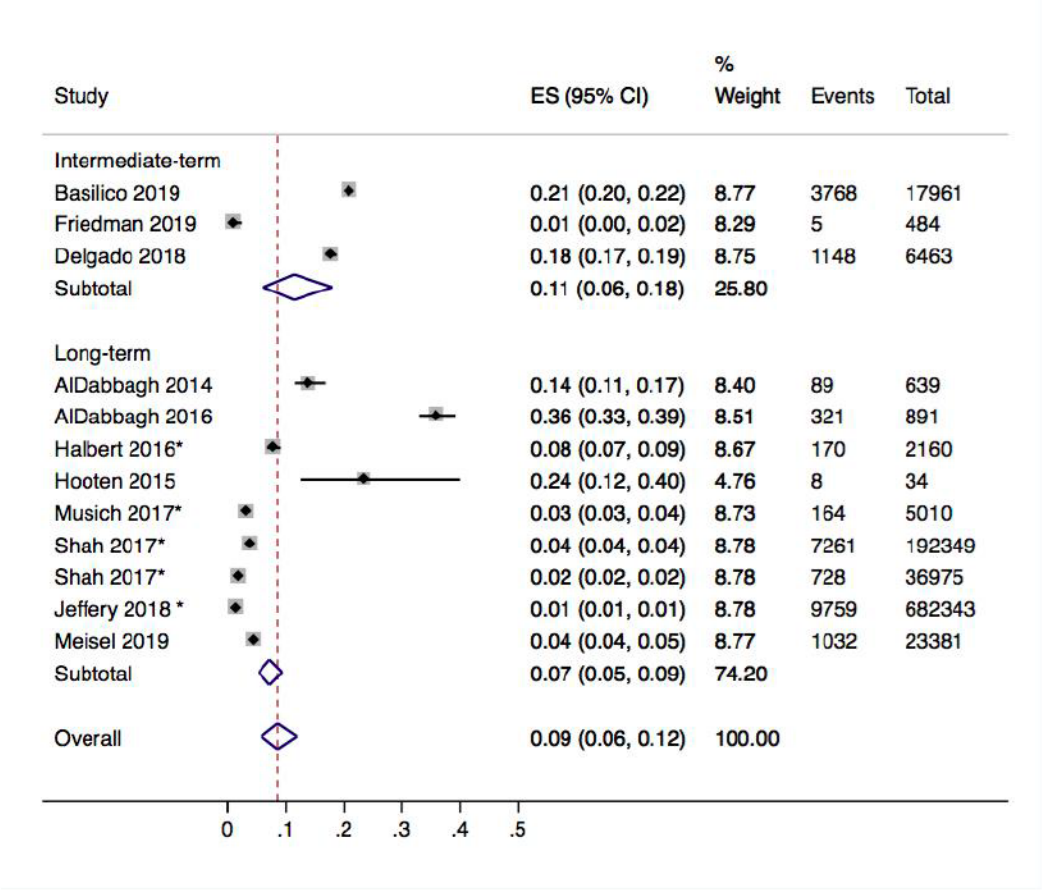
2-K-5: Study-specific and pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients receiving new opioids after injury, trauma, or ED presenting pain, analyzed by pain-type subgroup (random effects meta-analysis).



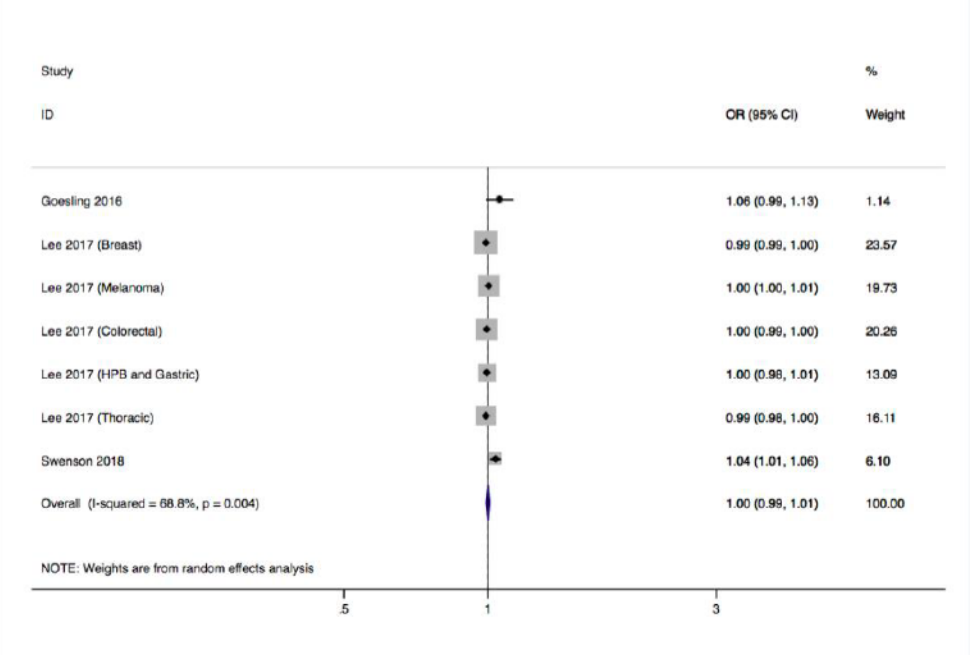
2-K-6: Study-specific and pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients receiving new opioids after surgery, analyzed by outcome timing subgroup (random effects meta-analysis).



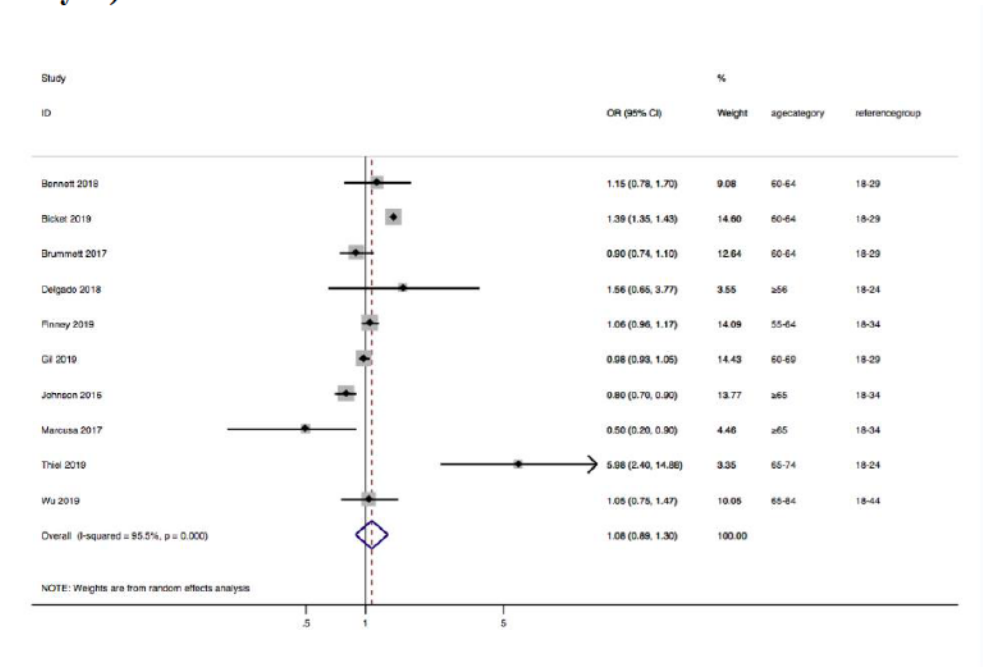
2-K-7: Study-specific and pooled risks (with 95% CI) of prolonged opioid use in opioid-naive patients receiving new opioids after injury, trauma, or ED presenting pain, analyzed by outcome timing subgroup (random effects meta-analysis).



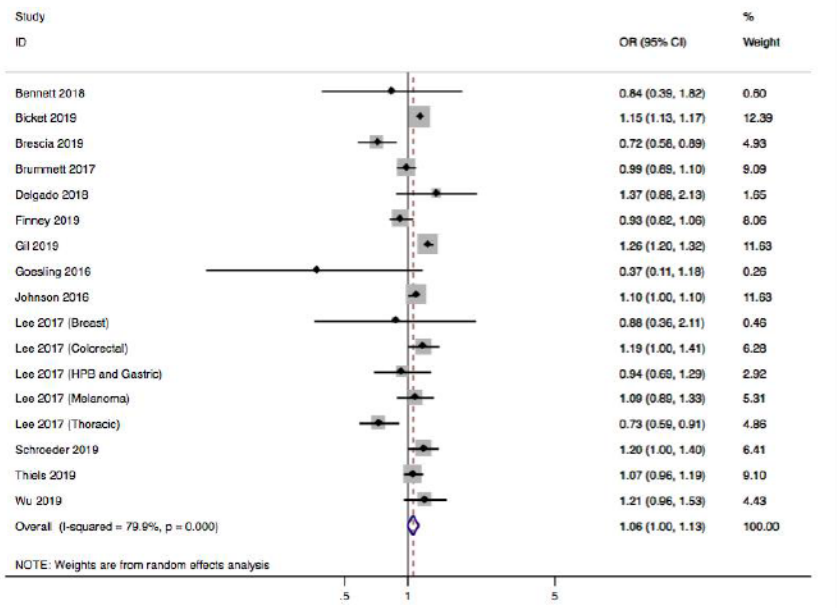
2-K-8: Study-specific and pooled odds ratios (with 95% CI) estimating the association between age (continuous) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



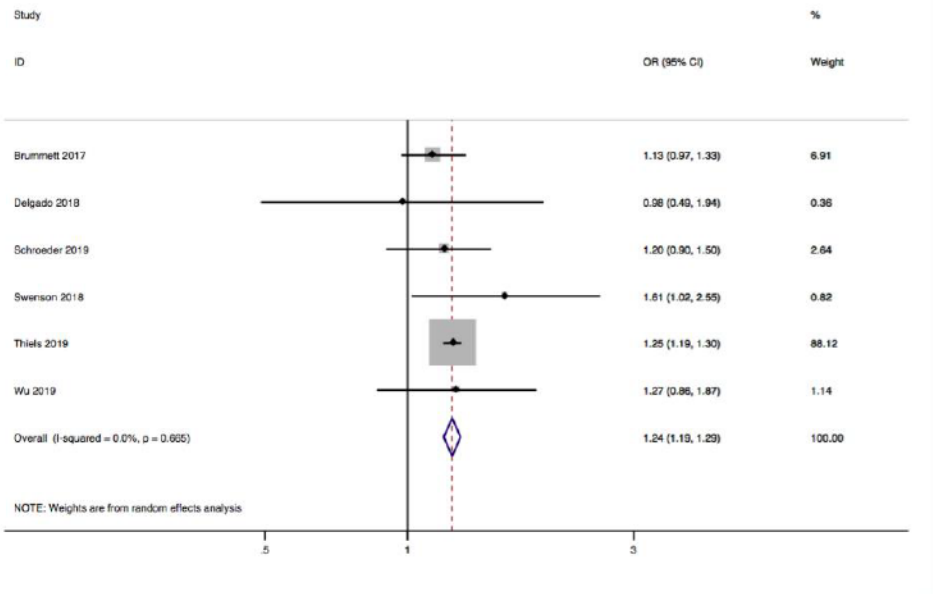
2-K-9: Study-specific and pooled odds ratios (with 95% CI) estimating the association between age (categorical, ≥ 60 y vs. 18-34y) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



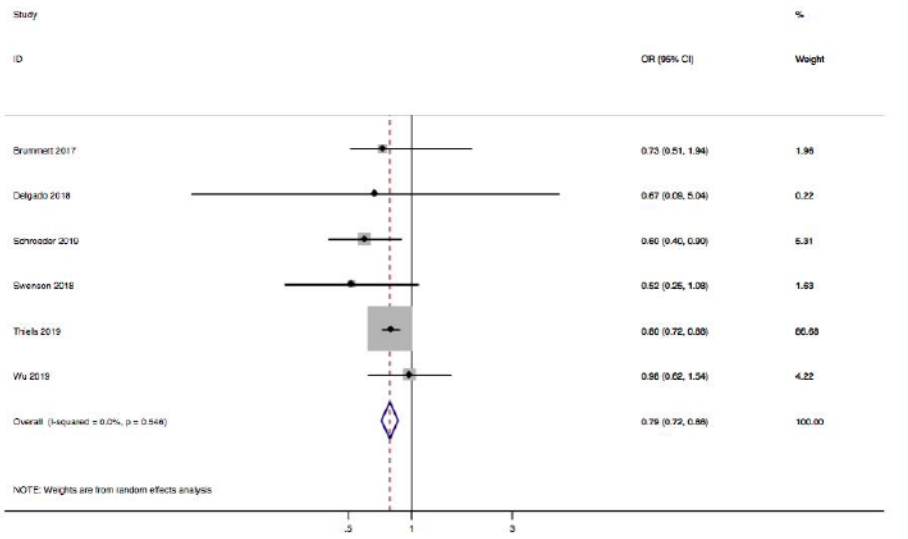
2-K-10: Study-specific and pooled odds ratios (with 95% CI) estimating the association between sex (female vs. male) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



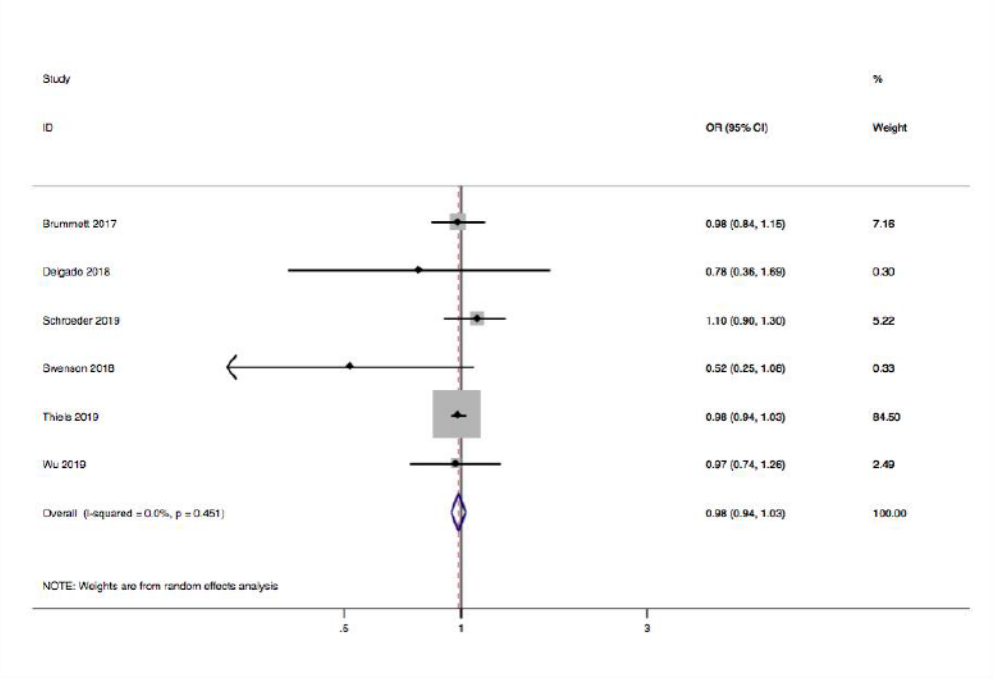
2-K-11: Study-specific and pooled odds ratios (with 95% CI) estimating the association between race (Black vs. white) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



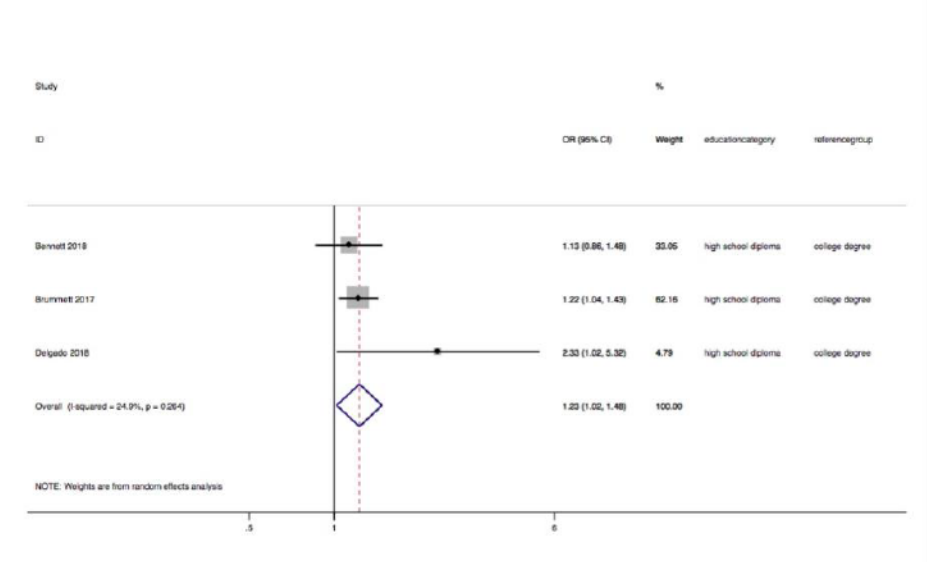
2-K-12: Study-specific and pooled odds ratios (with 95% CI) estimating the association between race (Asian vs. white) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



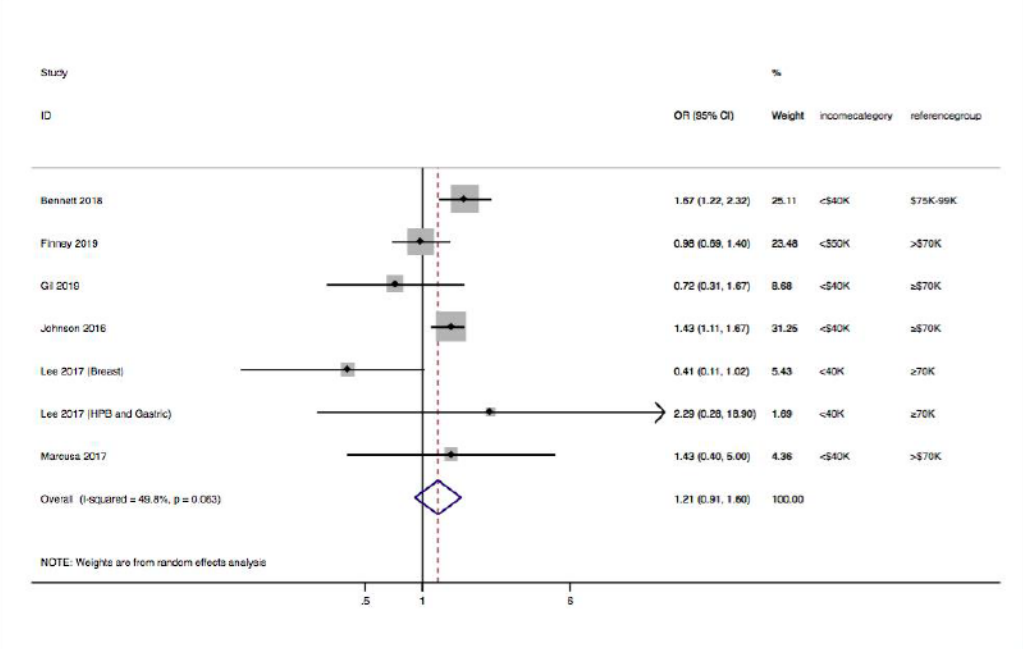
2-K-13: Study-specific and pooled odds ratios (with 95% CI) estimating the association between race (Hispanic vs. white) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



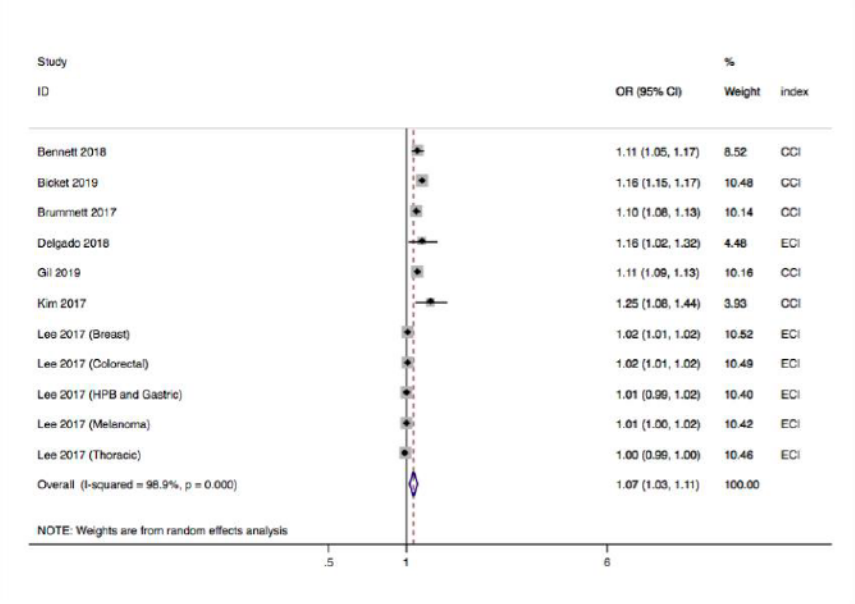
2-K-14: Study-specific and pooled odds ratios (with 95% CI) estimating the association between level of education (high school diploma vs. college degree) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



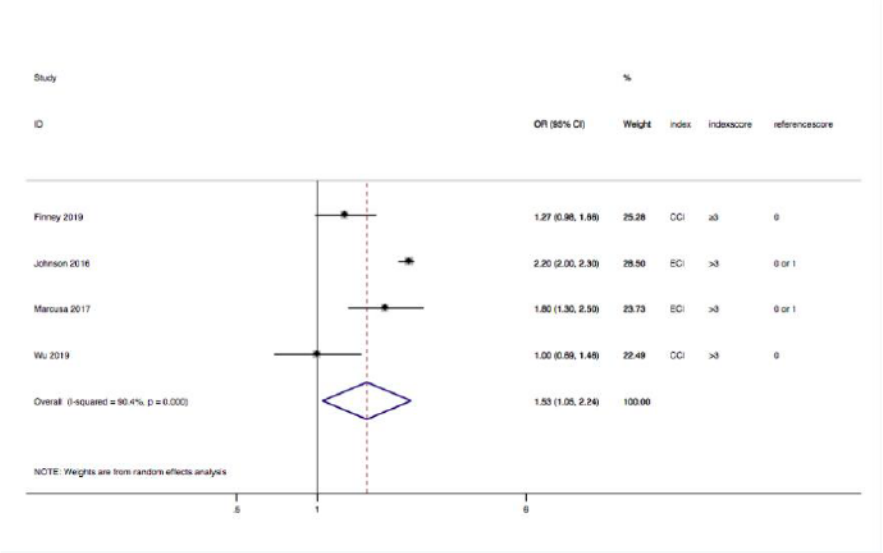
2-K-15: Study-specific and pooled odds ratios (with 95% CI) estimating the association between income (< 40K vs. ≥ 70K) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



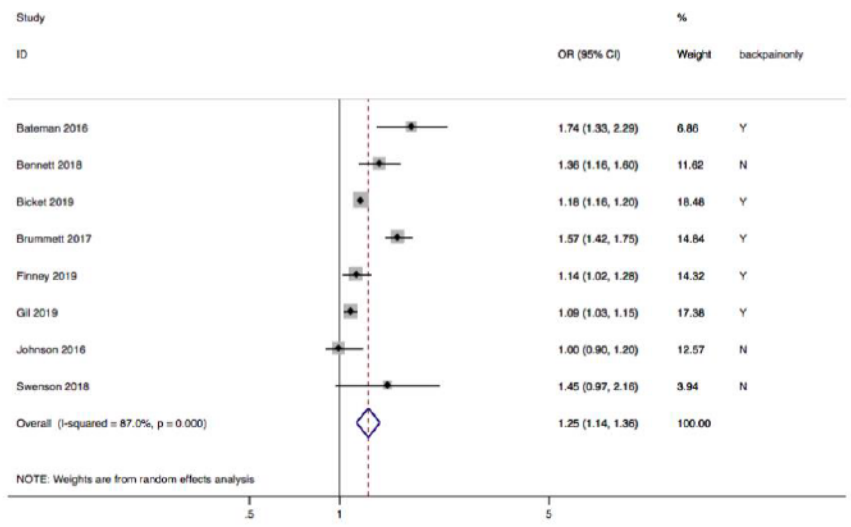
2-K-16: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of comorbidity (continuous, no.) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



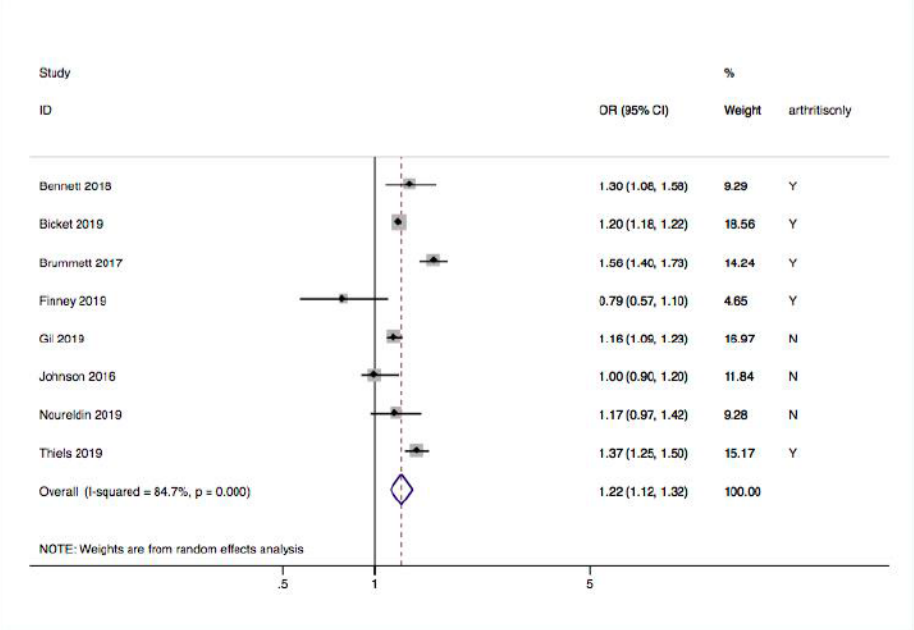
2-K-17: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of comorbidity (categorical, >3 vs. 0) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



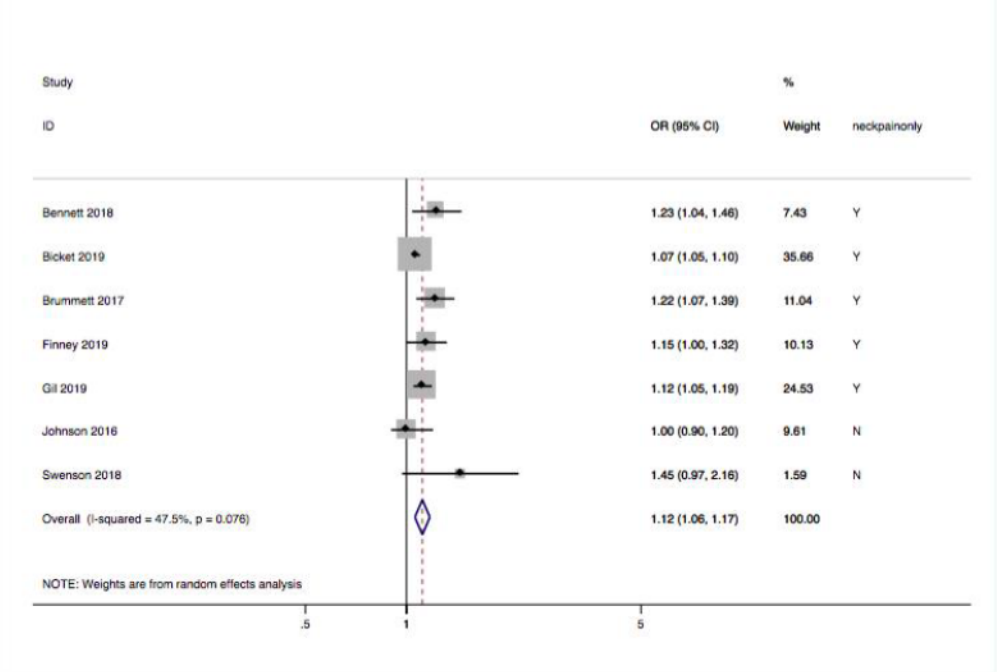
2-K-18: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of back pain (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



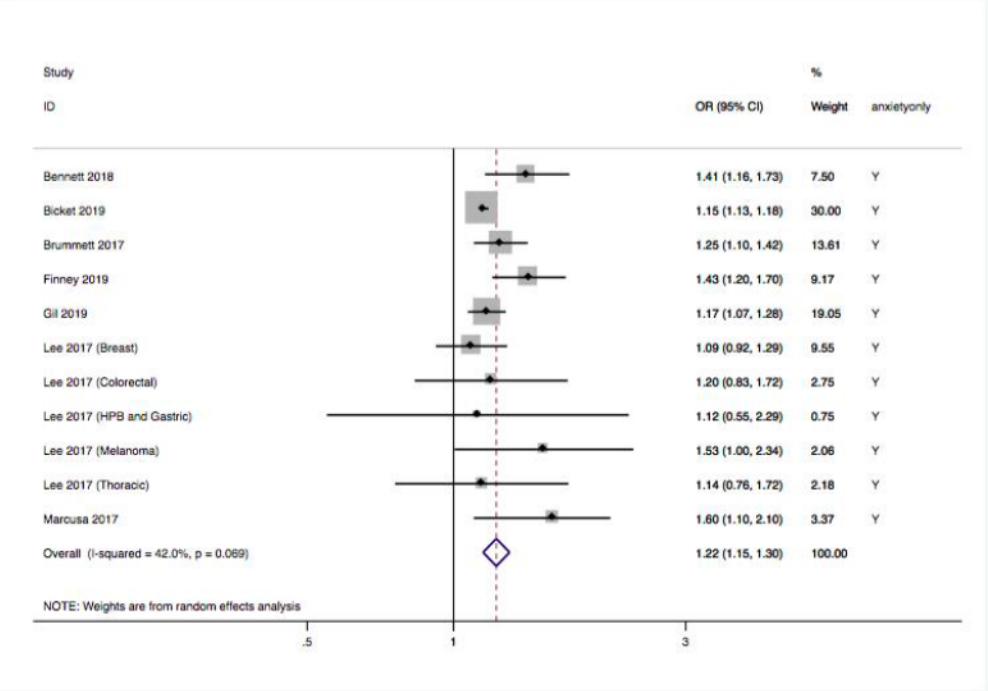
2-K-19: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of arthritis (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



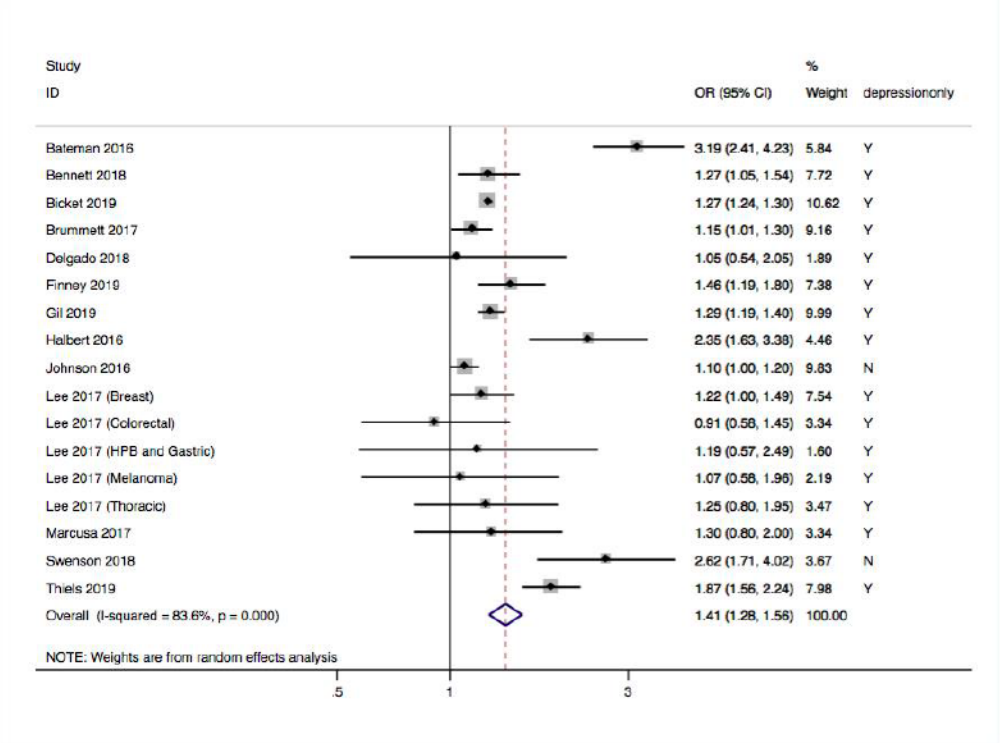
2-K-20: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of neck pain (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



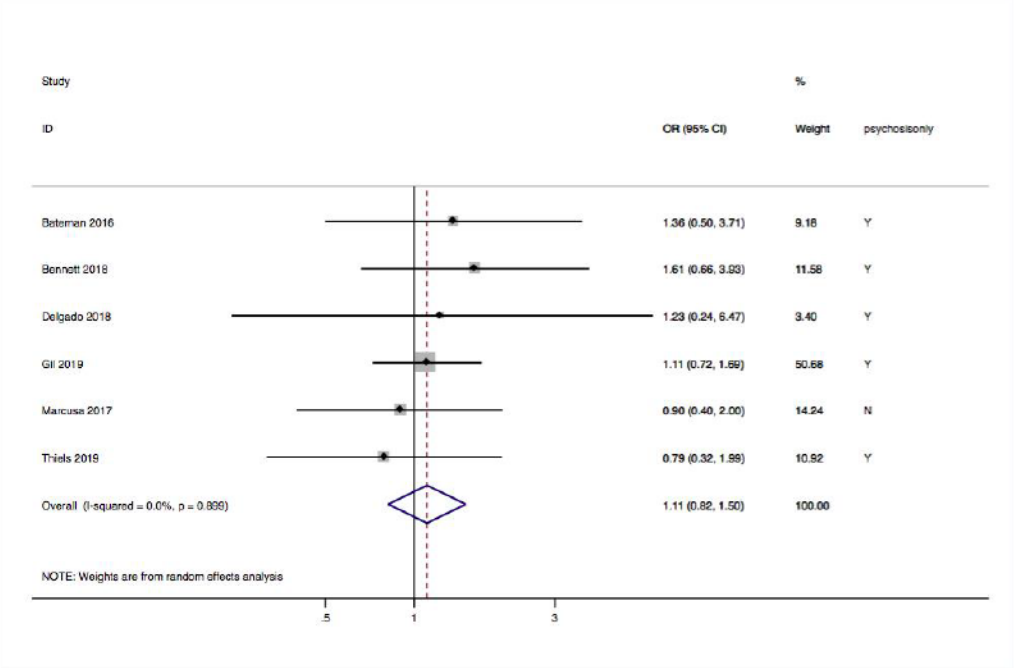
2-K-21: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of anxiety (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



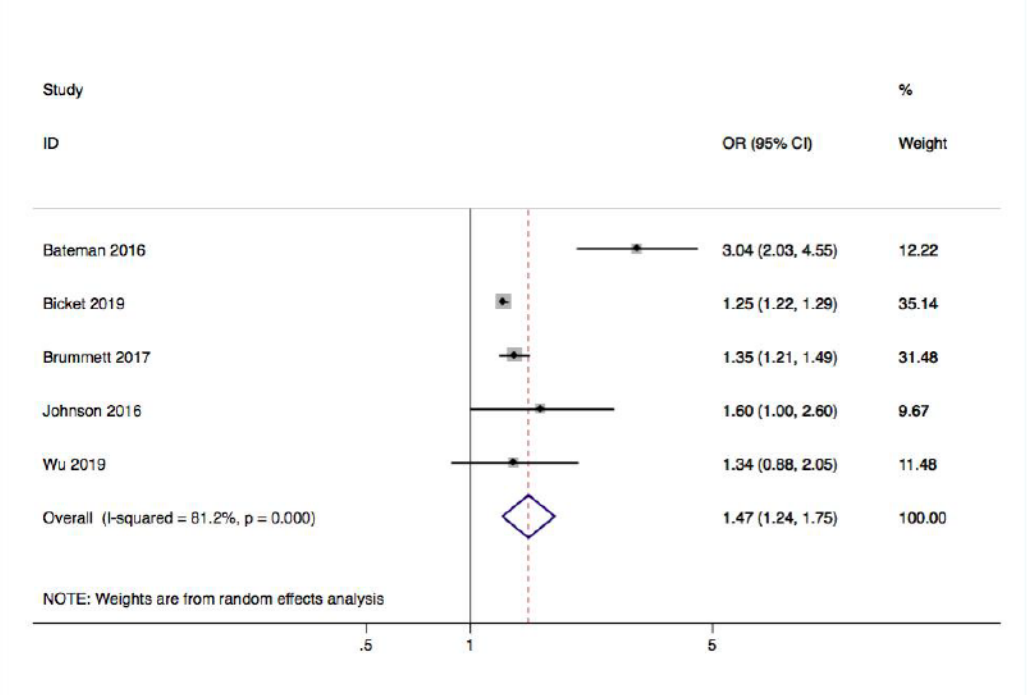
2-K-22: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of depression (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



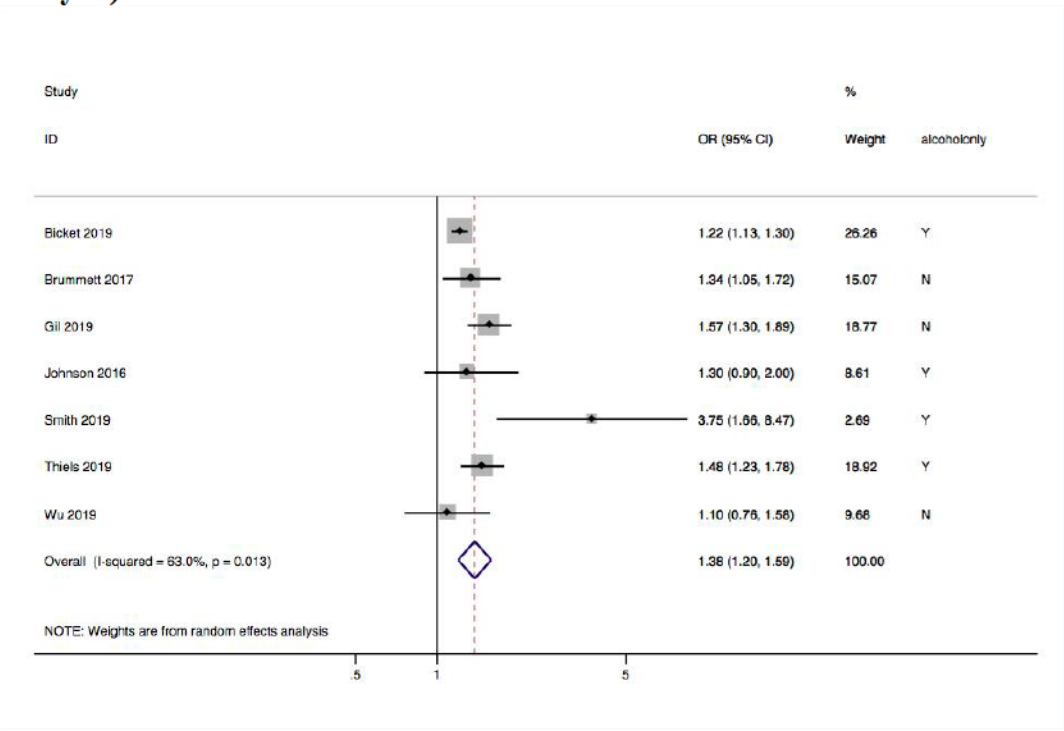
2-K23: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of psychosis (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



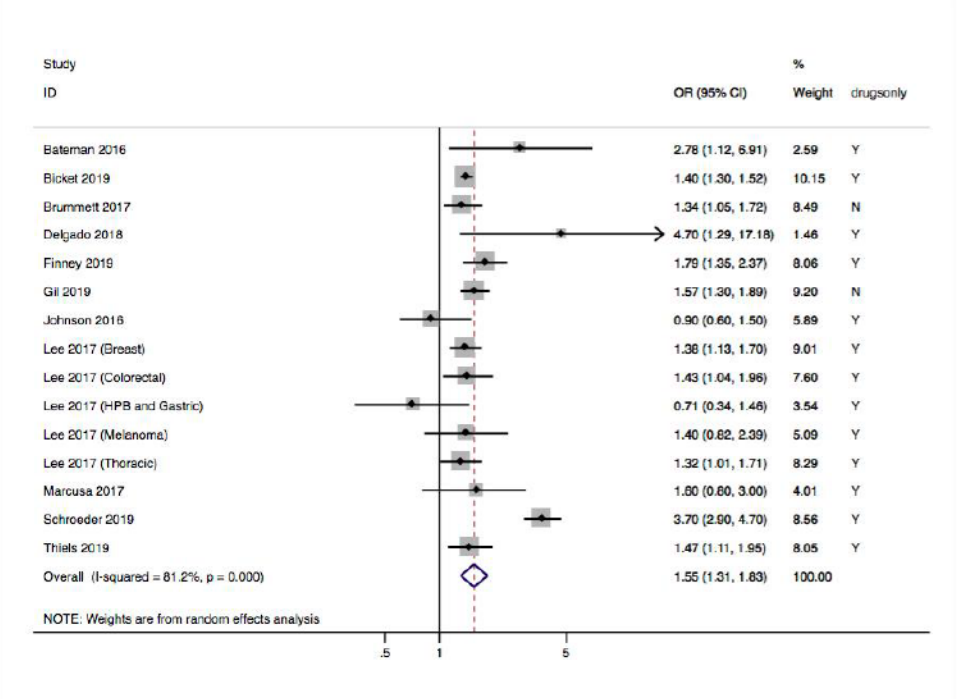
2-K-24: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of tobacco use (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



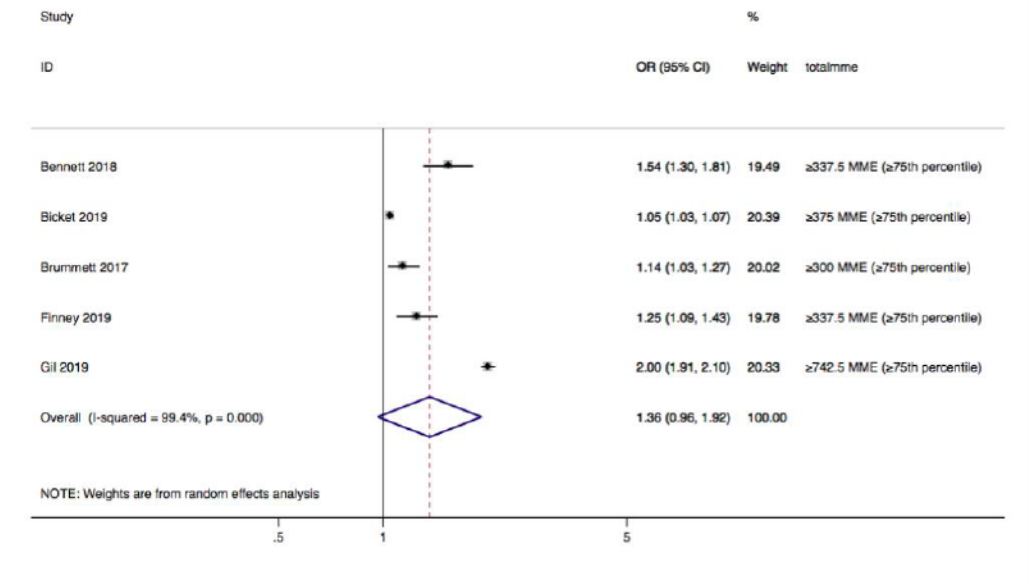
2-K-25: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of alcohol use (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



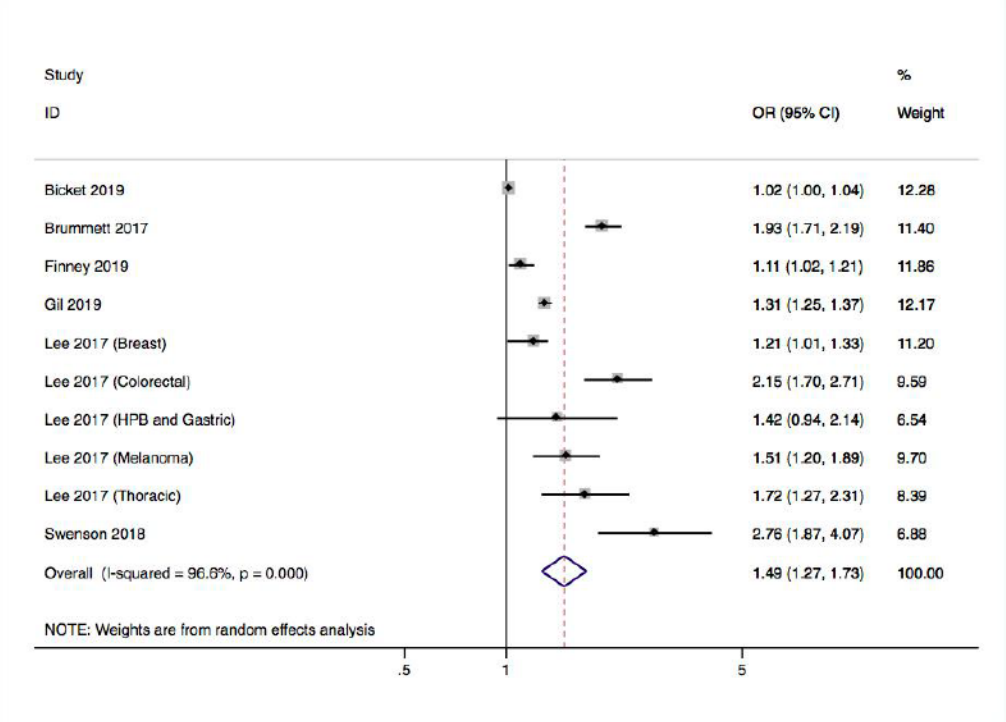
2-K-26: Study-specific and pooled odds ratios (with 95% CI) estimating the association between history of drug use (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



2-K-27: Study-specific and pooled odds ratios (with 95% CI) estimating the association between total perioperative MME (≥ 75th percentile vs. below) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



2-K-28: Study-specific and pooled odds ratios (with 95% CI) estimating the association between preoperative opioid fill* (yes vs. no) and prolonged opioid use in opioid-naive patients newly starting opioids for acute pain (random effects meta-analysis).



*Opioid filling in the 30 days prior to surgery (yes vs. no) in studies defining opioid-naivety as no opioid filling 12 months to 30 days prior to surgery, allowing new use to occur in the immediate pre-operative period.

Appendix 2-L Sensitivity Analyses

Sensitivity analysis (risks)

Outcome measurement

Including only studies that measured continuous or frequent use in the follow-up period, defined as a minimum of two or more opioid fills (or prescriptions or self-reported use), or a minimum of 90 days' supply:

After excluding studies that defined prolonged opioid use as a minimum of one opioid fill (or prescription or report of use) in the follow up period (i.e. not capturing continuous or frequent use), the pooled risk was 5% (95% CI 3% – 7%) in the surgery group (10 studies excluded: Bennett 2018, Bicket 2019, Brescia 2019, Brummett 2017, Finney 2019, Gil 2019, Goesling 2016, Johnson 2016, Lee 2017, and Marcusa 2017), 8% (95% CI 5% – 11%) in the injury, trauma, or ED presenting pain (one study excluded: Delgado 2018), and 2% (95% CI 2% – 3%) in the dental pain group (one study excluded: Shroeder 2019).

Study population

Including only studies with 100% of patients being opioid-naive at baseline, including only studies in which opioid use at baseline was objectively measured in 100% of included patients, excluding studies at high risk of bias. In the surgery group, excluding studies that included subjects who are not all opioid-naive (n=3): IP 7% (95% CI 5% – 10%), excluding studies that included subjects who did not all fill opioids at baseline (n=1): IP 7% (95% CI 5% – 9%) In the injury, trauma, or ED presenting pain group, all studies (or analyzed subgroups from studies) included subjects who were entirely opioid-naive and who filled or received opioid prescriptions at baseline.

Risk of bias

Excluding the two studies assessed to be at high overall risk of bias in the surgery group: IP 6% (95% CI 4 – 9). None of the studies in the injury group or the dental pain group were assessed to be at high risk of bias.

Sensitivity analysis (risk factors)

In the first analysis we restricted our analysis to studies with measures that did not include a combination of codes for clinical conditions and substance use (i.e. were specific to the factor under assessment). In the second analysis we only included studies with ideal adjustment, and in the third analysis we included only studies that were rated to be at low or moderate overall risk of bias.

Measurement

Back pain: Excluding studies using measure with codes for back pain + other conditions (n= 3): OR 1.27 (95% CI 1.14 – 1.41)
Arthritis: Excluding studies using measure with codes for arthritis + other conditions (n= 3): OR 1.28 (95% CI 1.11 – 1.46)

Neck Pain: Excluding studies using measure with codes for neck pain + other conditions (n= 2): OR 1.12 (95% CI 1.06 – 1.18)
Depression: Excluding studies using measure with codes for depression + other conditions (n=2): OR 1.41 (95% CI 1.28 – 1.56)
Psychosis: Excluding studies using measure with codes for psychosis + other conditions measured (n=1): OR 1.14 (95% CI 0.82 – 1.59)
Alcohol use: Excluding studies using measure with codes for alcohol use + other substance use (n=3): OR 1.41 (95% CI 1.13 – 1.78)
Drug use: Excluding studies using measure with codes for drug use + other substance use (n=2): OR 1.57 (95% CI 1.27 – 1.93)

Adjustment level: excluding studies with adjustment rated to be lower than 'ideal'

Age categorical: Excluding (n=7): OR 1.48 (95% CI 0.93 – 2.36)
Sex: Excluding (n= 14): OR 1.08 (95% CI 0.98 – 1.19)
Race Black: Excluding (n=4): OR 1.22 (95% CI 1.13 – 1.33)
Race Asian: Excluding (n=4): OR 0.80 (95% CI 0.72 – 0.88)
Race Hispanic: Excluding (n=4): OR 0.98 (95% CI 0.93 – 1.02)
Comorbidity continuous: Excluding (n= 9): OR 1.13 (95% CI 1.07 – 1.19)
Back pain: Excluding (n= 5): OR 1.45 (95% CI 1.13 – 1.86)
Arthritis: Excluding (n= 5): OR 1.36 (95% CI 1.16 – 1.60)
Neck pain: Excluding (n= 5): OR 1.12 (95% CI 0.99 – 1.27)
Anxiety: Excluding (n= 9): OR 1.17 (95% CI 1.09 – 1.25)
Depression: Excluding (n= 13): OR 1.66 (95% CI 1.26 – 2.20)
Psychosis: Excluding (n= 4): OR 1.01 (95% CI 0.52 – 2.00)
Tobacco use: Excluding (n= 2): OR 1.49 (95% CI 1.21 – 1.84)
Alcohol use: Excluding (n= 4): OR 1.31 (95% CI 1.15 – 1.49)
Drug use: Excluding (n= 11): OR 1.41 (95% CI 1.31 – 1.51)
Perioperative MME: Excluding (n= 3): OR 1.08 (95% CI 1.00 – 1.16); attenuated strength, but same direction and overall conclusion
Pre-operative fill: Excluding (n= 8): OR 1.40 (95% CI 0.75 – 2.61); same direction; potential loss of association (Bicket adjusted for periop. period dose, days supply, number of prescriptions; Brummett adjusted for periop MME; association observed may be driven by the overall quantity of opioids prescribed rather than timing [before or after surgery]).

Risk of bias: excluding studies at high risk of bias

Sex: Excluding n=2: OR 1.05 (95% CI 0.99 – 1.12)
Race (Black): Excluding n=2: OR 1.24 (95% CI 1.19 – 1.29)
Race (Asian): Excluding n=2: OR 0.81 (95% CI 0.73 – 0.89)
Race (Hispanic): Excluding n=2: OR 0.98 (95% CI 0.94 – 1.02)
Comorbidity categorical: Excluding n=1: OR 1.06 (95% CI 1.02 – 1.10)
Back pain: Excluding n=1: OR 1.24 (95% CI 1.13 – 1.36)
Arthritis: Excluding n=1: OR 1.22 (95% CI 1.12 – 1.34)
Neck pain: Excluding n=1: OR 1.11 (95% CI 1.06 – 1.16)

Depression: Excluding n=2: OR 1.34 (95% CI 1.22 – 1.48)
Alcohol use: Excluding n=1: OR 1.34 (95% CI 1.20 – 1.50)
Drug use: Excluding n=1: OR 1.43 (95% CI 1.31 – 1.55)
Preop. opioid filling: Excluding n=1: OR 1.42 (95% CI 1.21 – 1.65)

Appendix 2-M Detailed risk of bias assessment

Table: Detailed assessment of risk of bias in estimates of risk and effect estimates based on Iorio et al. and QUIPS tool criteria, respectively.

1		**Study ID: AlDabbagh_2014**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using Swedish National Hospital Discharge Register, the National Pharmacy Register, and the Total Population Register, all eligible subjects included (i.e. all hospitalized with tibia fractures within the study period and who did not use opioids in the period before the hospitalization were included.)
		Study Attrition	Low	Entire cohort analyzed
		Risk factor Measurement	Low	Same algorithms used for all subjects and identified in the Swedish National Hospital Discharge Register, the National Pharmacy Register, and the Total Population Register
		Outcome Measurement	Low	Outcome measured from National Pharmacy Register. Opioid use not ceased at 6 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m). And opioid use not ceased at 12 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m)
		Study Confounding	High	Suboptimal adjustment. Factors adjusted for: age, sex, type of fracture, mechanism of injury, and method of treatment
		Statistical Analysis and Reporting	Low	Cox proportional hazards model, event = opioid cessation (no prescription in 3 consecutive months of follow up)
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using Swedish National Hospital Discharge Register, the National Pharmacy Register, and the Total Population Register, all eligible subjects included (i.e. all hospitalized with tibia fractures within the study period and who did not use opioids in the period before the hospitalization were included.)
		Follow up was sufficiently long and complete	Low	Entire cohort analyzed
		Objective and unbiased measurement of prolonged opioid use was used	Low	Outcome measured from National Pharmacy Register. Opioid use not ceased at 6 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m). And opioid use not ceased at 12 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m)
2		**Study ID: AlDabbagh_2016**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using Swedish National Hospital Discharge Register, the National Pharmacy Register, and the Total Population Register, all eligible subjects included
		Study Attrition	Low	Entire cohort analyzed
		Risk factor Measurement	Low	Same algorithms used for all subjects and identified in the Swedish National Hospital Discharge Register, the National Pharmacy Register, and the Total Population Register
		Outcome Measurement	Low	Opioid use not ceased at 6 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m) and Opioid use not ceased at 12 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m)

		Study Confounding	High	Suboptimal adjustment. Factor adjusted for: age, sex, type of fracture, mechanism of injury
		Statistical Analysis and Reporting	Low	Cox proportional hazards model (unadjusted and adjusted), event = opioid cessation (no prescription in 3 consecutive months of follow up)
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using Swedish National Hospital Discharge Register, the National Pharmacy Register, and the Total Population Register, all eligible subjects included
		Follow up was sufficiently long and complete	Low	Entire cohort analyzed and median follow-up time was 20 (interquartile range [IQR] 16-102) months.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Opioid use not ceased at 6 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m) and Opioid use not ceased at 12 m. Opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months (F/U 6-24m)
3		**Study ID: Basilico 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	Data on all patients presenting to two American College of Surgeons (ACS) level I trauma centres with MSK trauma between 2002 - 2015 who underwent surgery and were eligible for inclusion were included
		Study Attrition	Moderate	Entire cohort analyze, but its unclear whether continuous enrolment was part of the inclusion criteria
		Risk factor Measurement	Low	Same algorithms used in the same datasets for RF measurement, obtained from institutional databases and research patient data registry
		Outcome Measurement	Low	Prolonged opioid use, which we identified as the receipt of at least one opioid prescription within 90 days of injury presentation and another within 90 to 180 days postoperatively. (Note: receiving opioid at discharge was part of the inclusion criteria)
		Study Confounding	Moderate	Minimum acceptable adjustment. Penalized for not including measures of history of psychiatric illnesses or substance use.
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	Data on all patients presenting to two American College of Surgeons (ACS) level I trauma centres with MSK trauma between 2002 - 2015 who underwent surgery and were eligible for inclusion were included
		Follow up was sufficiently long and complete	Moderate	Entire cohort analyze, but its unclear whether continuous enrolment was part of the inclusion criteria
		Objective and unbiased measurement of prolonged opioid use was used	Low	Prolonged opioid use, which we identified as the receipt of at least one opioid prescription within 90 days of injury presentation and another within 90 to 180 days postoperatively. (Note: receiving opioid at discharge was part of the inclusion criteria)
4		**Study ID: Bateman 2016**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using secondary data analysis, data on all eligible subjects were included.
		Study Attrition	Low	Study was restricted to patients with continuous enrollment with the insurer for at least 365 days prior to and 360 days after the beginning of follow-up.
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to caesarian delivery. Same algorithms used to measure RFs. RF validity and reliability not measured (but likely to be moderate - confirm), and opioid measures assume every patient used opioids as prescribed in full quantity at baseline.
		Outcome Measurement	Moderate	Outcome measured same way across participants but is data-driven

		Study Confounding	Low	Ideal adjustment which included demographic, clinical, and opioid factors
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using secondary data analysis, data on all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	One year follow up, every subject included had complete follow up data.
		Objective and unbiased measurement of prolonged opioid use was used	Moderate	Outcome is data-driven. Trajectory models, which group together patients with similar patterns of medication filling during follow-up were used to define the outcome. Based on this model, we defined the group of patients with the highest probability of filling over time as persistent users.
5		**Study ID: Bennett 2018**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study that used a national claims database, all eligible subjects were included in the study,
		Study Attrition	Low	Complete data for entire cohort. "We included only patients with continuous insurance coverage for 12 months before surgery and 6 months after surgery."
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to surgery. Same algorithms used to measure RFs. RF validity and reliability not measured (but likely to be moderate - confirm), dose assumes patient used baseline prescription as prescribed and used full quantity.
		Outcome Measurement	Low	New persistent opioid use, defined as continued prescription fills between 90 and 180 days after surgery. Subjects with additional procedures, Anastasia codes, or hospitalization in the FU period were excluded.
		Study Confounding	Moderate	Minimum acceptable adjustment. Penalized for not including opioid type or days supply.
		Statistical Analysis and Reporting	Low	multilevel logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study that used a national claims database, all eligible subjects were included in the study,
		Follow up was sufficiently long and complete	Low	6 months of follow up data. Complete for entire cohort.
		Objective and unbiased measurement of prolonged opioid use was used	Low	New persistent opioid use, defined as continued prescription fills between 90 and 180 days after surgery. Subjects with additional procedures, anesthesia codes, or hospitalization in the FU period were excluded.
6		**Study ID: Bicket 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using a national claims database, all eligible subjects were included in the study
		Study Attrition	Low	Data was complete for the entire cohort
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to surgery. Same algorithms used to measure RFs. RF validity and reliability not measured (but likely to be moderate - confirm), opioid factors assume patient used baseline prescription as prescribed and used full quantity.
		Outcome Measurement	Low	New persistent opioid use after procedures, as receipt of an opioid prescription between 90 and 180 days after the procedure. those without continuous or complete claims coverage in the 12 months after the procedure were excluded.

		Study Confounding	Low	Demographics (age, gender, year, region), occupational characteristics (employee status, wage type, union status), and clinical covariates (tobacco use, cancer diagnosis, CCI, mental health disorders, and pain diagnoses). The model also included the four perioperative opioid prescription characteristics: (1) prescription before procedures, defined as an opioid prescription fill within 30 days before the procedure, given past work suggesting this increases the odds of continued opioid use after surgery5; (2) total perioperative MMEs, defined as the total amount of opioid prescriptions filled 30 days before to 14 days after the procedure; (3) days' supply in the perioperative period, defined as the number of days covered with an opioid prescription; and (4) number of opioid prescriptions filled in the perioperative period.
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using a national claims database, all eligible subjects were included in the study
		Follow up was sufficiently long and complete	Low	One year follow up with complete data for the entire cohort.
		Objective and unbiased measurement of prolonged opioid use was used	Low	New persistent opioid use after procedures, as receipt of an opioid prescription between 90 and 180 days after the procedure. those without continuous or complete claims coverage in the 12 months after the procedure were excluded.
7		**Study ID: Brescia 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study that analyzed a national claims database, all eligible subjects were included.
		Study Attrition	Low	Entire cohort analyzed.
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to surgery. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm).
		Outcome Measurement	Low	Baseline fills present: yes; measured fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes; measurement period reflective of prolonged use (3m - 12m): yes
		Study Confounding	Moderate	Suboptimal adjustment: data-driven selection and missing opioid factors
		Statistical Analysis and Reporting	Moderate	Model building depended on p-values in unadjusted analysis.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study that analyzed a national claims database, all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	Follow up 6 months. Data complete for entire cohort as patients had to have continuous insurance enrollment for at least 1 year before and after surgery to be included.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes; measured fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes; measurement period reflective of prolonged use (3m - 12m): yes
8		**Study ID: Brummett 2017**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	The study sample captured every individual in the included database (Clinformatics Data Mart) meeting the inclusion criteria.
		Study Attrition	Low	All subjects who entered the study were analyzed. No loss to follow up (secondary data analysis). To be included patients must have had continuous insurance coverage during the 12 months before the procedure through the 6 months after.

		Risk factor Measurement	Moderate	To be included patients must have had continuous insurance coverage during the 12 months before the procedure through the 6 months after. The same algorithms were used to measure RFs for all subjects. Validity and reliability of co-morbidity measures not mentioned but known to be moderate.
		Outcome Measurement	Low	Outcome is measured using opioid fills for all subjects included. To be included patients must have had continuous insurance coverage during the 12 months before the procedure through the 6 months after.
		Study Confounding	Low	Models accounted for: surgery type, age, sex, race/ethnicity, education, history of tobacco use, mental health disorders, Charlson Comorbidity Index, pain disorders, and opioid prescription OME within the surgical time frame.
		Statistical Analysis and Reporting	Low	A multilevel, multivariate logistic regression model, with US Census Bureau geographic region included.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	The study sample captured every individual in the included database (Clinformatics Data Mart) meeting the inclusion criteria.
		Follow up was sufficiently long and complete	Low	All subjects who entered the study were analyzed. No loss to follow up (secondary data analysis). To be included patients must have had continuous insurance coverage during the 12 months before the procedure through the 6 months after.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Outcome is measured using opioid fills for all subjects included. To be included patients must have had continuous insurance coverage during the 12 months before the procedure through the 6 months after.
9		**Study ID: Carroll 2012**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	High	Unclear whether the 134 patients approached constitute all patients eligible for inclusion over the study period. No description of how non-participants differ from those who agreed to participate.
		Study Attrition	High	Unclear how many subjects were included in the final analysis. Unclear how many subjects, if any, were lost to follow up. No description of characteristics of those who may have been lost to follow up.
		Risk factor Measurement	Low	Validated measures were used on all subjects in the same manner to assess RFs; data collected prospectively
		Outcome Measurement	Moderate	Outcome measured by self-reported opioid discontinuation over the telephone.
		Study Confounding	High	Suboptimal adjustment
		Statistical Analysis and Reporting	Moderate	Multivariate model selection was accomplished using an automated stepwise algorithm for the selection of variables for the model. This was due to lack of prior literature to guide variable selection conceptually.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	High	The sample could differ systematically from the overall surgical population. For example, those agreeing to participate may have a baseline profile that is associated with lower risk of continuing opioid use.
		Follow up was sufficiently long and complete	High	Unclear how many subjects were included in the final analysis. Unclear how many subjects, if any, were lost to follow up. No description of characteristics of those who may have been lost to follow up.
		Objective and unbiased measurement of prolonged opioid use was used	Moderate	Outcome measured by self-reported opioid discontinuation over the telephone.
10		**Study ID: Delgado 2018**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	Population-based study including all eligible subjects included in large insurance claims database representative of the adult US population.
		Study Attrition	Low	Subjects were included in the outcome analysis only if they had a minimum of 6 m enrollment following the ED visit.

		Risk factor Measurement	Moderate	All included subjects had a minimum of 6 m data prior to ED visit. Same algorithms used to measure RFs. RF validity and reliability not measured (but likely to be moderate - confirm)
		Outcome Measurement	Moderate	Measurement relies on routinely collected data (is blind), but may overestimate rate of outcome by misclassifying those with fill between 30-60 days only as having prolonged opioid use
		Study Confounding	Moderate	Confounders measured: Age, sex, education level, race, comorbidity, year, alcohol abuse, drug abuse, depression, psychoses, state (fixed effects), MME, number of tablets, days supplied, and hydrocodone/oxycodone (latter 3 in sensitivity analysis).
		Statistical Analysis and Reporting	Low	A multilevel, multivariable logistic regression model was used.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	
		Follow up was sufficiently long and complete	Low	
		Objective and unbiased measurement of prolonged opioid use was used	Moderate	Including the period between 30-60 days may have introduced misclassification and resulted in over estimation of the outcome.
11		**Study ID: Deyo 2016**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using secondary data analysis, all eligible subjects are included.
		Study Attrition	Moderate	Unclear how many subjects did not have complete data because 12-m enrollment (insurance coverage) following the initiation month was not mentioned as an inclusion criteria. Unclear how they may have differed from the analyzed group.
		Risk factor Measurement	Low	Number of prescriptions and MME in the initiation month measured for all subjects from PDMP data.
		Outcome Measurement	Low	Six or more opioid fills during the subsequent year
		Study Confounding	High	Urban or rural residence and age categories are the only two factors accounted for as covariates in the multivariable analysis. Past opioid use exclusion criterion. Analysis stratified for opioid type (short vs. long-acting)
		Statistical Analysis and Reporting	Low	"We then conducted multivariable logistic regressions for the full cohort and relevant subsets, adjusting for urban or rural residence and age categories."
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Moderate for the non-cancer non-chronic pain subgroup; low for the dental subgroup	Non-cancer non-chronic pain was identified by excluding those < 45 years who did not die within 1 year of first prescription. This may have introduced misclassification of chronic pain and cancer patients for whom long-term opioid use was intended, thereby overestimating the risk.
		Follow up was sufficiently long and complete	Moderate	Data was analyzed for the entire baseline cohort, but because 12-m enrollment (insurance coverage) following the initiation month was not mentioned as an inclusion criteria, it is unclear whether data was complete for the entire cohort, and subsequently whether every subject had an equal change of having their outcome captured if it did occur. If many subjects lost enrolment (insurance) during the study follow up period, the outcome may have been underestimated.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Six or more opioid fills during the subsequent year

12		**Study ID: Finney 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using secondary data analysis, all eligible subjects are included.
		Study Attrition	Low	No loss to follow up because only subjects with continuous medical insurance enrollment during the 12 months before the surgical procedure through 6 months after were included.
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to ED visit. Same algorithms used to measure RFs. RF validity and reliability not measured (but likely to be moderate - confirm)
		Outcome Measurement	Low	New persistent opioid use, defined as fulfillment of an opioid prescription between 91 and 180 days after the surgical procedure
		Study Confounding	Moderate	Models adjusted for surgery type, patient characteristics including age, sex, mental health disorders, comorbidities, pain disorders, and opioid prescription OMEs within the perioperative period. Level of adjustment is minimum acceptable adjustment.
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	Patients from 18 to 64 years of age were identified who underwent surgical hallux valgus correction between January 2010 and June 2015
		Follow up was sufficiently long and complete	Low	Only subjects who had continuous medical insurance enrollment during the 12 months before the surgical procedure through 6 months after were included
		Objective and unbiased measurement of prolonged opioid use was used	Low	New persistent opioid use, defined as fulfillment of an opioid prescription between 91 and 180 days after the surgical procedure
13		**Study ID: Friedman 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	NA	No RF data included in primary study
		Study Attrition	NA	No RF data included in primary study
		Risk factor Measurement	NA	No RF data included in primary study
		Outcome Measurement	NA	No RF data included in primary study
		Study Confounding	NA	No RF data included in primary study
		Statistical Analysis and Reporting	NA	No RF data included in primary study
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	High	Unclear how included participants compare to the entire eligible cohort.
		Follow up was sufficiently long and complete	Low	6-month opioid prescription data available and analyzed for all 484 (100%) subjects.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Outcome included in the review analysis: Recurrent opioid use: filled >= 2 prescriptions within 6-mo period. Patients were followed by telephone 6 months after the ED visit and asked about opioid use in the previous week. Additionally, we reviewed the statewide prescription monitoring program database.
14		**Study ID: Gil 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using secondary data analysis, all eligible subjects are included.

		Study Attrition	Low	Patients without continuous enrollment during the 12months before and 6 months after surgery were excluded to ensure complete data collection.
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to ED visit. Same algorithms used to measure RFs. RF validity and reliability not measured (but likely to be moderate - confirm)
		Outcome Measurement	Low	prolonged opioid use, defined as >= 1 opioid prescription filled between 91 and 180 days after the surgical event
		Study Confounding	Moderate	Minimum acceptable adjustment, penalized for not including opioid type (short vs long acting)
		Statistical Analysis and Reporting	Low	Multivariable logistic regression including all variables conceptually chosen
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using secondary data analysis, all eligible subjects are included.
		Follow up was sufficiently long and complete	Low	Patients without continuous enrollment during the 12months before and 6 months after surgery were excluded to ensure complete data collection.
		Objective and unbiased measurement of prolonged opioid use was used	Low	prolonged opioid use, defined as >= 1 opioid prescription filled between 91 and 180 days after the surgical event
15		**Study ID: Goesling_2016**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	High	Unclear how many patients were eligible for inclusion and how those who participated may have systematically differed from those who did not. No flow chart.
		Study Attrition	Moderate	No information presented on participants lost to follow up. ~ 82% had data at the end of the study. Opioid-naive subgroup (for which outcome data is extracted and synthesized in this review): start n=407, end n=336 (~ 82%)
		Risk factor Measurement	Low	All participants completed a battery of self-report questionnaires preoperatively on the day of surgery.
		Outcome Measurement	High	Self-report at 6 months. Unclear how continuation of opioid use from baseline was assessed.
		Study Confounding	High	Unclear what covariates were included in the multivariable models.
		Statistical Analysis and Reporting	High	Multivariable logistic regression but model building and covariate included unclear.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	High	Unclear how many patients were eligible for inclusion and how those who participated may have systematically differed from those who did not. No flow chart.
		Follow up was sufficiently long and complete	Moderate	Six months follow up. No information presented on participants lost to follow up. ~ 82% had data at the end of the study. Opioid-naive subgroup (for which outcome data is extracted and synthesized in this review): start n=407, end n=336 (~ 82%)
		Objective and unbiased measurement of prolonged opioid use was used	High	Self-report at 6 months. Unclear how continuation of opioid use from baseline was assessed.
16		**Study ID: Hadlandsmyth_2017**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this study using the Veterans Health Administration HA datasets, all eligible subjects were included in the study
		Study Attrition	Low	Data analyzed for entire cohort. Every study subject has 12 months of data pre and post-surgery.
		Risk factor Measurement	Low	Same algorithms used for all subjects. Information of validity of algorithms used presented.

		Outcome Measurement	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes to both; measurement period reflective of prolonged use (3m - 12m): yes
		Study Confounding	Moderate	Minimum acceptable adjustment. Penalized for not including opioid factors (type, dose, days' supply)
		Statistical Analysis and Reporting	Low	Multivariable Poisson regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes to both; measurement period reflective of prolonged use (3m - 12m): yes
		Follow up was sufficiently long and complete	Low	Data analyzed for entire cohort. Follow up 12 months.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes to both; measurement period reflective of prolonged use (3m - 12m): yes
17		**Study ID: Halbert_2016**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Moderate	Nationally representative survey data. Baseline opioid use and acute pain reported within the same survey, but unsure whether they are directly related.
		Study Attrition	Low	Entire cohort analyzed. Only those with complete follow up data were included in the study.
		Risk factor Measurement	Moderate	ICD-9 codes used, but unclear if only after a condition was self-reported, and completeness of data unclear.
		Outcome Measurement	Moderate	Baseline fills present: yes; outcome measured as fills (not self-report): no; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes; measurement period reflective of prolonged use (3m - 12m): yes
		Study Confounding	High	Suboptimal adjustment. Penalized for not including baseline opioid factors.
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Moderate	nationally representative survey data. Baseline opioid use and acute pain reported within the same survey, but unsure whether they are directly related.
		Follow up was sufficiently long and complete	Low	Two years follow up.
		Objective and unbiased measurement of prolonged opioid use was used	Moderate	Self-reported opioid use
18		**Study ID: Hooten_2015**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	NA	No RF data included in review
		Study Attrition	NA	No RF data included in review
		Risk factor Measurement	NA	No RF data included in review
		Outcome Measurement	NA	No RF data included in review
		Study Confounding	NA	No RF data included in review
		Statistical Analysis and Reporting	NA	No RF data included in review

	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Moderate	Random sample (n= 293) selected from all eligible opioid-naive subjects who filled an opioid prescription during the study period (n=14,869), but no comparison of key baseline characteristics presented.
		Follow up was sufficiently long and complete	Moderate	1 year. Unclear whether data was available for all included subjects to classify use accurately
		Objective and unbiased measurement of prolonged opioid use was used	Moderate	Continuous prescribing over follow up period, but unclear whether continued enrolment was part of the inclusion criteria.
19		**Study ID: Jeffery 2018**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	NA	No RF data included in review
		Study Attrition	NA	No RF data included in review
		Risk factor Measurement	NA	No RF data included in review
		Outcome Measurement	NA	No RF data included in review
		Study Confounding	NA	No RF data included in review
		Statistical Analysis and Reporting	NA	No RF data included in review
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using a national claims database, all eligible subjects were included in the study
		Follow up was sufficiently long and complete	Low	One year, complete(100%), subjects were excluded from the study if they did not have 12 months enrolment (data) after the index fill.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes, ; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes to both; measurement period reflective of prolonged use (3m - 12m): yes.
20		**Study ID: Johnson 2016**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using national insurance claims database, all eligible subjects were included in the study.
		Study Attrition	Low	Entire cohort analyzed.
		Risk factor Measurement	Moderate	All included subjects had continuous enrolment during the study period. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm).
		Outcome Measurement	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	Moderate	Minimum acceptable adjustment. Penalized for not including opioid factors
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using national insurance claims database, all eligible subjects were included in the study.
		Follow up was sufficiently long and complete	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.

		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.
21		**Study ID: Karhade_2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	All eligible subjects were included in this secondary data analysis of electronic medical records.
		Study Attrition	Moderate	Entire cohort analyzed, but it is unclear whether follow up data was complete for all included subjects (i.e. continued enrolment)
		Risk factor Measurement	Low	Clear definitions, electronic health records, extent of missing data reported and methods of dealing with them reported.
		Outcome Measurement	Moderate	Baseline fills present: yes; outcome measured as fills (not self-report): no, prescriptions; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: unclear; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	Moderate	Minimum acceptable adjustment, penalized for not including baseline opioid prescription factors.
		Statistical Analysis and Reporting	Moderate	Predictive modeling. Selective reporting. On global model explanation, only most important predictors were presented. Only an example of individual patient-specific explanation for prediction generated by the stochastic gradient boosting model was presented.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	All eligible subjects were included in this secondary data analysis of electronic medical records.
		Follow up was sufficiently long and complete	Moderate	Six months follow up. Unclear whether follow up data was complete (or subjects with missing data were considered as not receiving prescriptions)
		Objective and unbiased measurement of prolonged opioid use was used	Moderate	Baseline fills present: yes; outcome measured as fills (not self-report): no, prescriptions; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: unclear; measurement period reflective of prolonged use (3m - 12m): yes.
22		**Study ID: Kim_2017**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using a national insurance claims database, all eligible subjects were included.
		Study Attrition	Low	Entire cohort analyzed. Patients were required to have 1-year continuous enrollment period after the index date
		Risk factor Measurement	Moderate	All included subjects had continuous enrolment during the study period. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm).
		Outcome Measurement	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	Moderate	Minimum acceptable adjustment. Penalized for not including baseline opioid prescription factors.
		Statistical Analysis and Reporting	High	Selective reporting of results (for the opioid-naive SG for which data is included in this review)
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using a national insurance claims database, all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	One year. Entire cohort analyzed. Patients were required to have 1-year continuous enrollment period after the index date

		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes; measurement period reflective of prolonged use (3m - 12m): yes.
23		**Study ID: Lee_2017**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using a national insurance claims database, all eligible subjects were included.
		Study Attrition	Low	Entire cohort analyzed
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to surgery. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm). Opioid dose assumes patient used full quantity as prescribed.
		Outcome Measurement	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no and yes; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	Moderate	Minimum acceptable adjustment, penalized for not including opioid type (short vs long acting)
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using a national insurance claims database, all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	Six months. 100% analyzed. Continuous insurance enrollment from 1 year before surgery to 1 year after surgery was required for inclusion.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no and yes; measurement period reflective of prolonged use (3m - 12m): yes.
24		**Study ID: Marcusa_2017**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study of a national insurance claims database, all eligible subjects were included in the study.
		Study Attrition	Low	Entire cohort analyzed.
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to surgery. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm).
		Outcome Measurement	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no and yes; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	Moderate	Suboptimal adjustment for lack of inclusion of baseline opioid prescription factors (dose, type, or days' supply).
		Statistical Analysis and Reporting	Low	Multivariable logistic regression
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study of a national insurance claims database, all eligible subjects were included in the study.
		Follow up was sufficiently long and complete	Low	120 days. Data complete for entire cohort ("We specified that patients included in this study had continuous enrollment in their insurance plan from the year before surgery, from which preoperative medication fills and comorbidities were obtained, through 120 days after, during which time all postoperative outcomes were obtained. ")
		Objective and unbiased measurement of	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with

		prolonged opioid use was used		subsequent healthcare encounters needing opioids: no and yes; measurement period reflective of prolonged use (3m - 12m): yes.
25		**Study ID: Meisel 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	NA	No RF data included in review
		Study Attrition	NA	No RF data included in review
		Risk factor Measurement	NA	No RF data included in review
		Outcome Measurement	NA	No RF data included in review
		Study Confounding	NA	No RF data included in review
		Statistical Analysis and Reporting	NA	No RF data included in review
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using claims data, all eligible subjects were included in the study
		Follow up was sufficiently long and complete	Moderate	12 months. Unclear whether continued enrolment in FU period is part of the inclusion criteria
		Objective and unbiased measurement of prolonged opioid use was used	Low	>= 1 prescription fill in every calendar quarter. Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no and yes; measurement period reflective of prolonged use (3m - 12m): yes.
26		**Study ID: Musich 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	NA	No RF data included in review
		Study Attrition	NA	No RF data included in review
		Risk factor Measurement	NA	No RF data included in review
		Outcome Measurement	NA	No RF data included in review
		Study Confounding	NA	No RF data included in review
		Statistical Analysis and Reporting	NA	No RF data included in review
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using insurance claims database, all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	12-months FU. 100% of cohort had complete data. 12-month continuous medical and drug plan enrollment follow-up after opioid initiation through December 2017.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Chronic opioid use was defined as >= 2 prescriptions and>90 days' supply of opioids. Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
27		**Study ID: Noureldin 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using a national insurance claims database, all eligible subjects were included in the study.
		Study Attrition	Low	Data was available for the entire cohort.

		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to surgery. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm).
		Outcome Measurement	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	High	Unclear which covariate were adjusted for in the final presented model. No inclusion of opioid factors (dose, type, days' supply).
		Statistical Analysis and Reporting	Moderate	Multivariable Cox proportional hazards model with variables selected for inclusion based on statistical significance in univariate analysis.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using a national insurance claims database, all eligible subjects were included in the study.
		Follow up was sufficiently long and complete	Low	12 months of follow up. Outcome data was available for the entire cohort.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Persistent opioid use in opioid-naïve patients which was defined as opioid prescribed 90-365 days following the index IBD flare. Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids:no; measurement period reflective of prolonged use (3m - 12m): yes.
28		**Study ID: Roughead 2019**		

		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	NA	No RF data included in primary study
		Study Attrition	NA	No RF data included in primary study
		Risk factor Measurement	NA	No RF data included in primary study
		Outcome Measurement	NA	No RF data included in primary study
		Study Confounding	NA	No RF data included in primary study
		Statistical Analysis and Reporting	NA	No RF data included in primary study
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study of administrative health claims database from the Australian Government Department of Veterans' Affairs (DVA), all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	90 days, data complete for entire cohort as all included subjects were gold card holders who have full lifetime access to both public and private healthcare services.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Chronic opioid users was defined as those who continued taking opioids for greater than 90 days post discharge.
29		**Study ID: Shah 2017**		

		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study of insurance claims databases, a 10% random sample of eligible subjects were included.
		Study Attrition	Moderate	Unclear whether continuous enrolment in the follow up period was part of the inclusion criteria.
		Risk factor Measurement	Low	Unbiased measure of opioid type, dose, days' supply, and indication for opioids.
		Outcome Measurement	Low	Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.

		Study Confounding	Low	Ideal adjustment. Although all patients whose demographic information including type of payer, age, sex, and geographic region were missing or invalid were excluded, the % was <2%
		Statistical Analysis and Reporting	Low	Cox proportional hazards model
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Moderate	Acute pain assumed from no prior chronic pain diagnosis.
		Follow up was sufficiently long and complete	Moderate	One year. Unclear whether continuous enrolment in the follow up period was part of the inclusion criteria.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Opioid discontinuation was defined as at least 180 continuous days without opioid use from the end date of the last opioid prescription. The date of discontinuation was defined as the end date of the last opioid prescription before 180 opioid free days. Baseline fills present: yes; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
30		**Study ID: Shoenfeld_2017**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using the Military Health System Data Repository (MDR), all eligible subjects were included in the study.
		Study Attrition	Low	Follow up data complete for entire cohort.
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to surgery. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm).
		Outcome Measurement	Low	Baseline fills present: yes (84%); outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	Moderate	Minimum acceptable adjustment, penalized for not including index opioid factors.
		Statistical Analysis and Reporting	Low	Cox proportional hazard model
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using the Military Health System Data Repository (MDR), all eligible subjects were included in the study. All underwent surgery. All opioid naive. 84% filled an opioid after surgery. All adult.
		Follow up was sufficiently long and complete	Low	One year. Follow up data complete for entire cohort.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Continuous opioid use over 6 months (no lapses lasting > 30 days), and continuous opioid use over 12 months (no lapses lasting > 30 days). Baseline fills present: yes (84%); outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
31		**Study ID: Shroeder_2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study including a national insurance claims database, all eligible subjects were included.
		Study Attrition	Low	Complete data for entire cohort.
		Risk factor Measurement	Moderate	All included subjects had a minimum of 12 m data prior to first prescription. Same algorithms used to measure RFs. RF validity and reliability not measured for substance abuse (but likely to be moderate - confirm).

		Outcome Measurement	Low	Baseline fills present: yes ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	High	Although chronic conditions in the previous 12 months is mentioned as an exclusion criterion in Figure 1, it's unclear which conditions were included or how they were measured. Suboptimal adjustment, penalized for not including index opioid factors and co-morbidities other than non-opioid substance abuse.
		Statistical Analysis and Reporting	Low	Multivariable logistic regression.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study including a national insurance claims database, all eligible subjects were included. All acute pain. All filled an opioid at baseline. All opioid-naive. Average age 21 years (SD 2.4). Patients with complex chronic conditions in 12 months before prescription or hospitalized 7 days before were excluded.
		Follow up was sufficiently long and complete	Low	One year. Complete data for entire cohort.
		Objective and unbiased measurement of prolonged opioid use was used	Low	At least 1 additional filled opioid prescription at 90 to 365 days after the initial prescription. Baseline fills present: yes ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.

32		**Study ID: Smith 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Moderate	Unsure what % of eligible patients over the study period were included.
		Study Attrition	Moderate	Study depended on EMR review. Unclear what % had complete outcome data, but entire cohort analyzed.
		Risk factor Measurement	Moderate	Data on RF factors abstracted from EMRs. % of missing data unknown.
		Outcome Measurement	High	Variability in measurement. Prescriptions identified through departmental radiation oncology and hospital-wide electronic medical record (EMR) systems. No other sources of opioid prescribing captured.
		Study Confounding	High	Suboptimal adjustment. Only variables that were statistically significant in univariate analysis were included in the final model.
		Statistical Analysis and Reporting	High	In multivariable analysis, the models were fit using data with complete information of covariates selected from univariable analysis and the outcome. Stepwise selection with Akaike information criterion (AIC) was conducted to find the best combination of covariates selected from univariable analysis.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Moderate	Unsure what % of eligible patients over the study period were included.
		Follow up was sufficiently long and complete	Moderate	Six months. Study depended on EMR review. Unclear what % had complete outcome data, but entire cohort analyzed.
		Objective and unbiased measurement of prolonged opioid use was used	High	Variability in measurement.

33		**Study ID: Swenson 2018**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study of insurance claims database, all eligible subjects were included.
		Study Attrition	Low	Data complete for entire cohort.

		Risk factor Measurement	Moderate	All included subjects had 8 months continuous enrolment before their procedure. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm).
		Outcome Measurement	Low	Baseline fills present: yes ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	High	Suboptimal adjustment, penalized for not including baseline opioid factors.
		Statistical Analysis and Reporting	Moderate	Multivariable logistic regression (hierarchical). Variable inclusion depended on statistical significance.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study of insurance claims database, all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	Six months. Data complete for entire cohort. Subjects were included only if they had continuous insurance enrollment from 8 months prior to hysterectomy through the 6 month post hysterectomy time period.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
34		**Study ID: Thiels 2019**		
		Domain	**Risk of bias level**	**Support for judgement**
	Effect Estimate	**Study Participation**	Low	In this population based study using national insurance claims database, all eligible subjects were included.
		Study Attrition	Low	Complete data for the entire cohort.
		Risk factor Measurement	Moderate (low for opioid factors)	All included subjects had 6 months continuous enrolment before their procedure. Same algorithms used to measure RFs. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm). Opioid measures unbiased.
		Outcome Measurement	Low	Baseline fills present: yes (80%) ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
		Study Confounding	Low	ideal adjustment
		Statistical Analysis and Reporting	Low	Multivariable logistic regression.
	Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this population based study using national insurance claims database, all eligible subjects were included.
		Follow up was sufficiently long and complete	Low	Six months. Complete data for the entire cohort. The analyses of chronic opioid use included patients with any post-surgery opioid fill and at least 180 days of uncensored follow-up.
		Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes (80%) ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: yes and no; measurement period reflective of prolonged use (3m - 12m): yes.
35		**Study ID: Wu 2019**		
		Domain	**Risk of bias level**	**Support for judgement**

Effect Estimate	**Study Participation**	Low	In this clinical population study using integrated healthcare system health records, all eligible subjects were included in the study.
	Study Attrition	Low	Complete follow up data for entire cohort.
	Risk factor Measurement	Moderate	All included subjects had 6 months continuous enrolment before their procedure. Some RFs measured using data in medical records and some using ICD codes with the same algorithms used for all subjects. RF validity and reliability not measured for co-morbidities (but likely to be moderate - confirm). Opioid measures unbiased.
	Outcome Measurement	Low	Baseline fills present: yes (80%) ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.
	Study Confounding	Moderate	Minimum acceptable adjustment, penalized for not including opioid type.
	Statistical Analysis and Reporting	Low	Multivariable logistic regression
Risk Estimate	**The sample of patients in the study was well defined and representative of the target population**	Low	In this clinical population study using integrated healthcare system health records, all eligible subjects were included in the study.
	Follow up was sufficiently long and complete	Low	Six months. Complete follow up data for entire cohort. Only patients with at least 180 days' continuous membership after discharge were included in subsequent analysis of opioid use following hospitalization.
	Objective and unbiased measurement of prolonged opioid use was used	Low	Baseline fills present: yes (80%) ; outcome measured as fills (not self-report): yes; measure of continuation (not one fill) OR excluded subjects with subsequent healthcare encounters needing opioids: no; measurement period reflective of prolonged use (3m - 12m): yes.

3 Chapter Three: Methods for Objectives 2 and 3

3.1 Note to reader

The datasets used in Aims 2 and 3 were made available by Health Data Nova Scotia (HDNS) and were funded by a PhD Bursary from the Saudi Arabian Cultural Bureau in Canada. Staff at HDNS linked six routinely collected administrative databases to identify the study cohort and obtain the requested study variables. For the purposes of data description, I refer to the individual studies for Aims 2 and 3 collectively as 'the study' where appropriate. I make distinctions between the two Aims whenever necessary.

3.2 Data sources

In the province of Nova Scotia, Canada, several routinely collected administrative databases are made available to researchers through the health data repository Health Data Nova Scotia (HDNS), Dalhousie University. To access data, researchers are required to submit a data access form that includes details about the study objectives, design, analysis plan, potential impact, as well as ethical considerations for the research project. Forms are reviewed by a dedicated committee and, if the access request is approved, researchers must show proof of funding and ethics approval. Research staff at HDNS then link the requested databases using unique encoded identifiers and assemble a de-identified dataset(s) for the research team to access. The dataset(s) are accessed on a secure remote portal for analysis.

For Aims 2 and 3 of this thesis, I requested data linkage across the following seven databases, of which data from one was later excluded as described below: (1) The Drug Information System (DIS), (2) Medical Services Insurance (MSI) Physician's Billings (3) Canadian Institute of Health Information (CIHI) Discharge Abstract

Database (DAD), (4) CIHI National Ambulatory Care Reporting System (NACRS), (5) Licensed Provider Registry, (6) Insured Patient Registry (MASTER), and (7) Vital Statistics (VITAL). See Table 3.1 for a description of each database. Study subjects were initially identified from the DIS database (i.e., by having filled an opioid prescription during the study period), and then filtered by applying the inclusion and exclusion criteria, as described below, using information from the DIS, MSI Physicians' Billings, CIHI DAD, and NACRS databases. Data on study variables were obtained from the same four databases as well as the: (1) Licensed Provider Registry for prescriber variables, (2) Insured Patient Registry for sociodemographic variables, and (3) Vital Statistics for death during follow-up.

Two datasets were created. The first dataset included information about the study cohort. The second dataset included information about opioid prescriptions that were filled by subjects included in the cohort during the study follow-up period. I merged the two datasets for data cleaning, reorganization according to the study aims, and analyses using the statistical analysis and data science software Stata, version15.[1]

Prescriber data from the Licensed Provider Registry database were missing for 24.1% of included subjects. No information about possible reasons for missing data were available to guide me in creating an imputation plan that would account for the most likely types of missing data. The degree of potential bias introduced by including these data in the analysis was assessed to be high; hence these data were excluded from the thesis. As such, Aim 2 was based on data obtained from five of the linked databases (i.e., DIS, MSI, DAD, NACRS, and MASTER) while Aim 3 was based on all six remaining linked databases (i.e., excluding Licensed Provider Registry).

Table 3-1: Data sources

	Database	Population	Description of data included and purpose*	Dates requested	Used to identify cohort	Used to obtain data for study variables
1	**Drug Information System (DIS)**	All individuals, excluding military, filling prescriptions from physicians in Nova Scotia community pharmacies.	Data on all prescriptions filled in a community pharmacy in Nova Scotia. DIS data are collected by Nova Scotia Department of Health and Wellness (DHW) and are a part of Nova Scotia's electronic health record (EHR) system.	October 28, 2016 (earliest available date) to March 31, 2019 Data from October 28, 2016 to April 25, 2017 were used to determine opioid-naivety status only	√ Identify opioid fills, determine naivety status, identify formulations for exclusion	√ Date of index fill, all prescription data
2	**MSI Physician's Billings (MSI)**	All individuals, excluding military, receiving billable services from physicians in Nova Scotia.	Contains records for each insured service encounter rendered by a physician and paid for by the Nova Scotia Medical Services Insurance (MSI). This dataset is created and maintained by Medavie Blue Cross for the Nova Scotia DHW. It is gathered and used for administrativ	January 26, 2016 (to obtain data about co-morbidities in the 12 months preceding the index prescription) to March 31, 2019	√ Identify codes for procedures to determine eligibility	√ Data on patient chronic pain, mental illness, substance abuse, and cancer diagnoses + type of procedure, billing specialty of procedure provider.

			e and auditing purposes.			
3	**CIHI Discharge Abstract Database (DAD)**	All individuals, excluding military, discharged from acute care facilities which submit data to the DAD	DAD captures administrative, clinical, and demographic information on hospital discharges. Data are collected by the Canadian Institute for Health Informatics (CIHI). CIHI collects data and makes it available to stakeholders to support decision making in health care, health system performance, and population health.	January 26, 2016 (to obtain data about comorbidities in the 12 months preceding the index prescription) to March 31, 2019	√ Identify codes for procedures to determine eligibility	√ Data on patient chronic pain, mental illness, substance abuse, and cancer diagnoses
4	**CIHI National Ambulatory Care Reporting Systems (NACRS)**	All individuals, excluding military, receiving ambulatory/emergency care, as well as day surgeries	NACRS contains data for all hospital-based and community-based ambulatory care: day surgery, outpatient and community-based clinics, and emergency departments. CIHI collects data and makes it available to stakeholders	January 26, 2017 to March 31, 2019	√ Identify codes for ED visit	√ Date of visit to calculate time from visit to fill

			to support decision making in health care, health system performance, and population health.			
5	**Insured Patient Registry (MASTER)**	Entire population of insured health care beneficiaries in Nova Scotia.	MASTER contains demographic, geographic, and insurance (eligibility start/end dates, termination status and reason) information on the entire population of insured healthcare beneficiaries in Nova Scotia. It is used for administrative purposes by the Nova Scotia DHW.	January 26, 2017 to March 31, 2019	√ Determine whether subject is ≥18 years of age on day of fill	√ Age and sex variables
6	**Vital Statistics (VITAL)**	Deceased Nova Scotians in Nova Scotia.	Data about death is gathered by Statistics Canada and obtained by the Nova Scotia DHW.	January 26, 2017 to March 31	√ (Aim 3 only) Determine death status during follow-up	No

*As described on Health Data Nova Scotia website

3.3 Study design and cohort selection

I used a population-level, cross-sectional design for **Objective 2**. The study population included opioid-naive adults in Nova Scotia, Canada who filled new opioid

prescriptions from community pharmacies after surgical or emergency care. With data from five included databases, study design allowed me to take a 'snapshot' of subjects, characteristics of their first filled prescriptions, their demographic and clinical characteristics on the day of filling, the acute care setting that the prescription likely originated from, and for those who had a procedure, the type of procedure performed – in broad categories – and the billing specialty of the procedure provider. For **Objective 3**, I used a population-level, retrospective cohort design. The study included a subgroup from the cohort included in Objective 2, as described below. Each included subject was followed up for six months from the first filled prescription. Data from the six included databases allowed me to determine baseline demographic and clinical characteristics of included subjects, characteristics of their first filled prescription, and the type of acute care for which the prescription likely originated. I was then able to review the data prospectively to determine whether the outcome had occurred for each subject included in the cohort.

To select the study cohort used in **Objective 2**, I began by identifying all opioid prescriptions that were filled in community pharmacies in Nova Scotia, Canada between April 26, 2017, and March 31, 2019, by adults ≥18 years of age. All opioid formulations and corresponding drug information numbers (DINs) are presented in the Appendix 3-A. From all identified prescription fills, I excluded:

1. Those who had another opioid prescription filled in the preceding 180 days, to ensure each included subject met the study definition of opioid naivety.
2. Fills for formulations used to treat cough, diarrhea, or opioid use disorder

3. Fills for subjects who did not have 12 months (365 days) of active insurance enrolment in the 12-month look-back period, to ensure comorbidity data for covariate analysis was complete for all included subjects. We identified enrolment status from the Insured Patient Registry database
4. Fills that were not preceded by at least one code for a surgical procedure or at least one visit to the emergency department (ED) in the preceding 14 days. We included all Canadian Classification of Procedures (CCP) codes from the MSI Physicians' Billing's Database and Canadian Classification of Health Interventions (CCI) codes from CIHI DAD to identify surgical procedures. We used a broad definition of surgical procedures that included obstetrical care and some interventional procedures that are carried out by internal medicine specialties. We identified ED visits using a code from the NACRS database that captures leaving the ED. The choice of 14 days aligns with previous studies that have considered opioid fills occurring within that period to be within the peri-operative period (i.e., likely directly related to the surgical event).[2,3] For the full list of codes, see Appendix 3-B.

For subjects who had multiple opioid prescription fills meeting the above criteria, the earliest fill was selected for inclusion in the study, and the date of the fill was considered the index date. All subsequent fills, except those occurring on the same day, were considered to have occurred during follow-up. Consequently, each included subject was represented only once in the cohort. Those with multiple fills on the index day were also represented only once, with data concerning all fills retained in the database. Selection of

the initial study cohort was performed by HDNS staff. I applied additional exclusions, post-hoc, as follows:

1. For those who had additional prescription opioid fills during follow-up, I excluded subjects who filled formulations used to treat opioid use disorder (i.e., methadone and buprenorphine/naloxone) in the first three follow-up fills, as they were considered unlikely to be opioid naive at baseline (<0.5% of eligible subjects).
2. Those whose prescriptions were >30 days' supply, as I considered them unlikely to be treated for acute pain, and those whose prescriptions were ≥200MME/day, considered unlikely to be opioid naive at baseline (<1% of eligible subjects).

For a schematic representation of study cohort selection, see Figure 3-1.

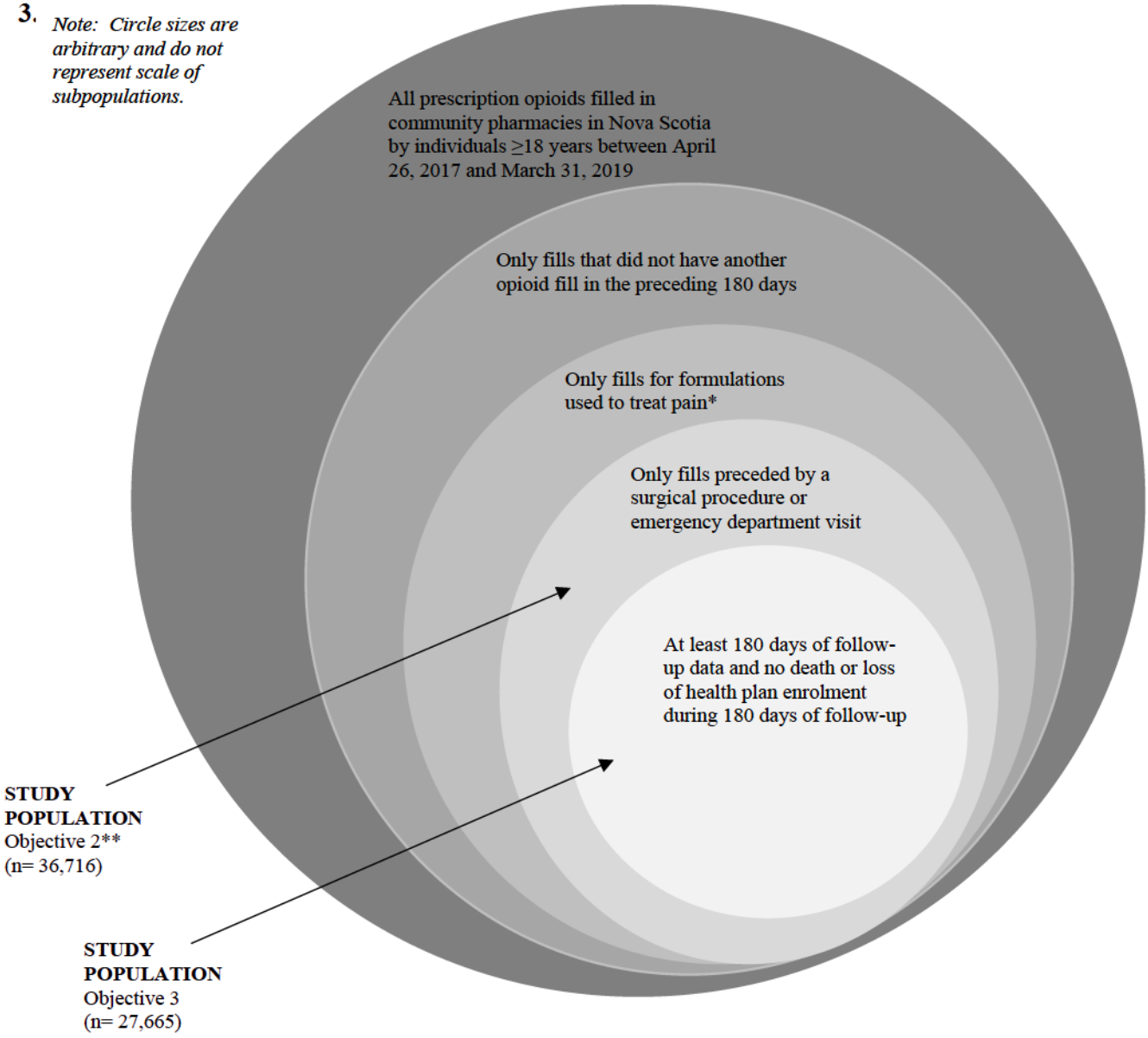
For **Objective 3**, I applied the following additional exclusion criteria:

1. Subjects with less than six months (180 days) of follow-up data, as identified from the DIS database.
2. Subjects who died during the six months of follow-up, as identified from vital statistics.
3. Subjects who lost their health plan insurance during the six months of follow-up, as identified from the Insured Patient Registry database.

For a schematic representation of study design and cohort selection Objective 3, see Figure 3-2.

Figure 3-1: Schematic representation of study cohort selection for Objectives 2 and 3.

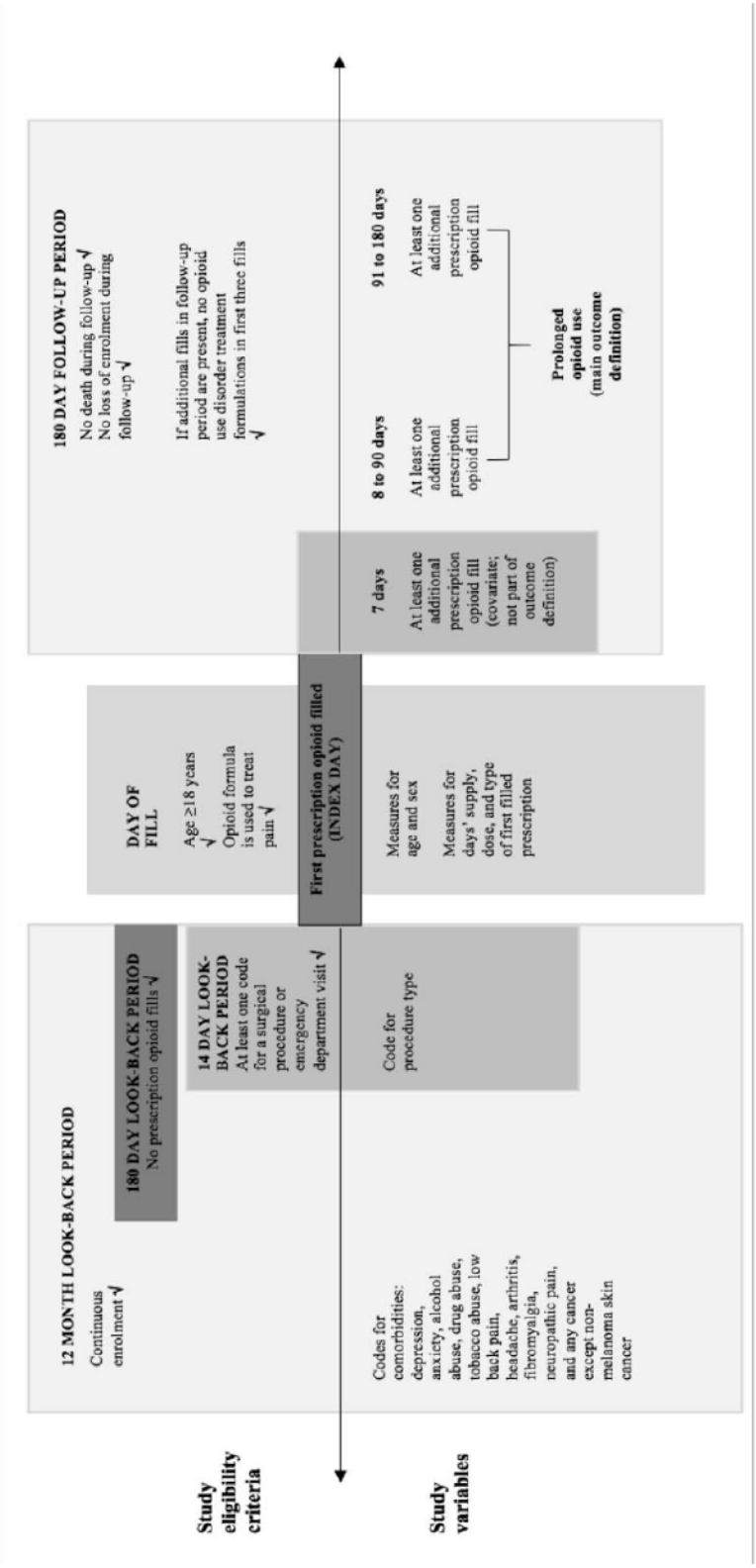
Note: Circle sizes are arbitrary and do not represent scale of subpopulations.



*We excluded prescription opioids used to treat cough, diarrhea, or opioid use disorder

** Additional exclusions: Opioid use disorder treatment filled in first 3 subsequent fills, if applicable. Prescription >30 days' supply and >200MME/day. No continuous health plan enrolment in 12-months look-back period (to ensure data for covariate analysis is complete for all subjects).

Figure 3-2: Schematic representation of study design, cohort selection criteria, and included variables for Objective 3



3.4 Study variables and data management

Variables that were included in the analysis for Objectives 2 and 3 were either the same as, or derived from, the variables included in the initial study datasets assembled by HDNS. A complete list of variables requested from HDNS is presented in the Appendix 3-C.

3.4.1 Objective 2 variables:

Three groups of variables were included in the analysis for Objective 2: (1) prescription related variables to achieve the descriptive objective of Objective 2 and to derive the study outcomes; (2) exposure variables that measured the setting and the specialty of the procedure provider for those who had surgical procedures; and (3) covariates that were adjusted for in the analysis, which included patient characteristics and, for the subgroup that had surgical procedures, the type of procedure performed.

Baseline prescription variables and study outcomes

To describe prescribing patterns, I derived the following variables from the dataset about every included fill: i) opioid type, which I categorized into codeine, hydromorphone, oxycodone, morphine, tramadol, or other; ii) route of administration (oral or other); iii) days' supply of prescription (included in the DIS dataset as '*expected use time'* which is calculated by the pharmacist), which I included both as a continuous variable and categorized into ≤3 days, 4 to 7 days, and >7 days for description; iv) total and average daily dose of prescription, which I measured in morphine milligram equivalents (MME), calculated using the formula and conversion factors provided by the Ontario Drug Policy Research Network [4]; and v) whether there were multiple opioid prescriptions filled on the index day. For subjects with multiple fills on the index day,

data about all prescriptions that were filled were considered. Dose in MME was summed across all the fills, and the longest days' supply was considered for the days' supply variable and as the denominator for calculating dose per day. Long-acting formulations were prioritized when both short- and long-acting formulations were filled on index day.

I derived the following binary variables (yes, no) to measure primary study outcomes: prescription >7 days' supply, prescription ≥90 MME/day, prescription for long-acting opioid; and secondary outcomes: prescription for strong opioid, and prescription for tramadol. Hydromorphone, oxycodone, morphine, and fentanyl were considered strong opioids, while codeine and tramadol were considered weak opioids. I also derived variables to measure the primary outcomes defined using alternative thresholds: prescription >3 days' supply, prescription >14 days' supply, prescription ≥ 50 MME/day because these thresholds are sometimes used to measure long days' supply and high-dose prescribing.

Exposure variables

To estimate the strength and direction of association between the care setting and the study outcomes for the entire study population, I created three mutually exclusive setting groups based on the identified codes in the 14-day look-back period: surgical care, emergency care, or emergency plus surgical care. Subjects were considered to have had surgical care only if they had at least one procedure code with no ED visit codes during the look-back period, and emergency care only if they had at least one ED visit code with no procedure codes during the look-back period. Subjects were included in the emergency plus surgical care group if they had at least one ED visit and one procedure code in the look-back period.

To assess the association between provider specialty and the study outcomes for the subgroup who had surgical procedures, regardless of emergency care status (i.e., those who were included in either the surgical care or emergency plus surgical care groups), I derived a variable to determine the specialty of the procedure provider. This variable was derived from the MSI Physicians' Billings database, and the categories created were: general surgery, orthopedic surgery, plastic surgery, otolaryngology, urology, other surgical specialties (cardiac, neuro, thoracic, and vascular surgery), general practice, and non-surgical, non-general practice specialties including medical and interventional radiology specialties. Surgical specialty can be used as a proxy for common training and clinical experiences among physician groups, and exploring differences in prescribing across its groups may shed light on potential drivers of variation that relate to the prescriber rather than the patient.

Covariates

I requested data on patient characteristics to describe the study population and to adjust for patient characteristics in the analysis. The variables included subject age (continuous variable), sex (male, female), and 12-month medical history of a group of comorbidities, namely: depression, anxiety disorder, alcohol abuse, drug abuse, low back pain, headache/migraine, arthritis/joint pain or neck pain, fibromyalgia, neuropathic pain, and cancer. Data about age and sex were obtained from the Insured Patient Registry database, and data about comorbidity were obtained from the MSI Physicians' Billings and CIHI DAD databases. The diagnostic code variable (dxcode1-25) from the CIHI DAD was used to identify International Classification Diseases 10th edition (ICD-10-CA) diagnostic codes corresponding to each of the comorbidities selected. The diagnostic

code variable (dxcode1-3) from the MSI Physicians' Billings was used to identify International Classification Diseases 9th edition (ICD-9-CM) diagnostic codes. For each comorbidity, subjects were coded as 'yes' if they had at least one corresponding ICD code documented in the included databases. See Appendix 3-D for a complete list of codes. All variables measuring comorbidity were derived by staff at HDNS using the list of codes provided to them in my data request.

To adjust for procedure type in the analysis assessing the association between procedure provider specialty and study outcomes, I also derived a procedure type variable based on data obtained from the Physicians' Billings database capturing Canadian Classification of Procedure codes. I categorized the procedure type variable into the following: major surgery; minor surgery; fracture, dislocation, or cast; bone grafting; obstetrics procedures; and other, which included procedures that were captured in the DAD but not the Physicians' Billings database. When a subject had multiple procedures during the 14-day look-back period, I used the procedure that was most proximal to the prescription fill date to create the variable. The choice of covariates was informed by previous research, which found that physicians who prescribe opioids are often influenced in their prescribing decisions by expected behaviors of the patient and potential consequences.[5] Patients' age, sex, history of psychiatric conditions, drug abuse, chronic pain, and cancer diagnoses may all affect prescribers' perceived perception about future behaviors and consequences related to prescription opioid use. Among the surgical care subgroup, the type of procedure is also expected to influence prescribing decisions for pain management.[6]

3.4.2 Objective 3 variables

Three groups of variables were included in the analysis for Objective 3: (1) exposure variables about the first prescription filled, namely: dose, days' supply, and whether the formulation was for a long-acting opioid; (2) outcome variables about the quantity of prescriptions filled during follow-up, if any, and their dates; and (3) variables that measured covariates that were adjusted for in the analysis, including patient characteristics and whether additional opioid prescriptions were filled during the first week of follow-up. Data about patient characteristics were also used to describe the included study population.

Exposure variables

For each included subject, I used data obtained from the DIS database about the filled prescription on index day: the formulation, strength, quantity, and expected use time of the prescription, as calculated by the pharmacist. I used these data to derive exposure variables, which were average daily dose of first filled prescription (continuous variable), days' supply of first filled prescription (continuous variable), and whether the prescription was for a short- or long-acting formulation (binary variable). To calculate dose, I used the Ontario Drug Policy Research Network[4] guide to calculate the MME of the included prescription(s). The formula multiplies the strength of the formulation by the quantity dispensed, then multiplies it by a conversion factor for the formulation. To calculate MME/day, I divided total MME by the number of days supplied. Days' supply was derived from the *expected use time* variable included in the DIS, which measures days of expected use of the filled prescription as calculated by the pharmacist. I considered extended-release, long-acting, and sustained-release formulations to be long

acting. For subjects with multiple fills on index day, I summed the doses across all filled prescriptions and chose the longest days' supply filled. When both short- and long-acting formulations were filled, I prioritized the long-acting formulation in exposure variables.

Outcome variables

Data about the quantity and date of all prescriptions filled by each subject during the study follow-up period was used to derive the study outcome, prolonged opioid use. The primary definition of prolonged opioid use was having filled ≥1 opioid prescription(s) from 8 to 90 days from the index date and ≥1 additional prescription(s) from 91 to 180 days. I constructed a binary variable after management of follow-up data to determine, for each included subject, whether their outcome status was yes or no. I derived three additional variables to measure alternative definitions of prolonged use. A less conservative definition considered a subject to have had prolonged use if they had ≥1 fills in the period from 91 to 180 days from index date. A more conservative definition considered prolonged use with ≥4 fills, with at least one in each of 8 to 90, 91 to 180, 181 to 270, and 271 to 365 days. A third definition was based on the American Society for Enhanced Recovery and Perioperative Quality Initiative (POQI-4) joint consensus statement on persistent perioperative opioid use, which considered a subject to have had prolonged use if they had ≥1 fills in the period from 91 to 365 days, with at least 60 days' supply.[7] After creating these outcome variables, I transformed the data structure of the follow-up dataset such that each subject had only one row of data (i.e., from long to wide format). I then merged the transformed dataset with the baseline cohort dataset using unique study identification numbers.

Covariates

I included variables about patient characteristics and other factors that have previously been shown to be associated with prolonged opioid use in opioid-naive populations after surgical and emergency care[2,8-11], as well as a directed acyclic graph proposing the relationship between first-prescription factors and opioid-related harms[12], a conceptual framework about unintended prolonged opioid use[13], and clinical input. I included variables measuring age (continuous variable), sex (male, female), and a medical history of mental illnesses (yes if a code for depression and/or anxiety was present), history of substance abuse (yes if a code for alcohol abuse and/or drug abuse was present), history of tobacco abuse (yes if at least one code for tobacco abuse was present), history of chronic pain conditions (yes if a code for at least one of the following conditions was present: low back pain, arthritis, neck pain, headache, fibromyalgia, or neuropathic pain), history of cancer (yes if a code for any cancer diagnosis except non-melanoma skin cancer was present). I also derived a variable measuring whether additional opioid prescriptions were filled in the first seven days (0, 1, ≥2), as additional opioid prescription fills in the first week after an initial prescription has been shown to be associated with prolonged use,[14] and I wanted to assess risk independently of this factor.

3.5 Statistical analysis

3.5.1 Analysis for Objective 2

To describe characteristics of the study sample and filled prescriptions, I summarized continuous, normally distributed variables using means and standard deviations, and skewed variables using medians and interquartile ranges. I summarized categorical variables using frequencies and percentages. To estimate the prevalence of study outcomes (i.e., prescription fills >7 days' supply, ≥90 MME/day, and long-acting opioid

formulations), I calculated the proportion of those with the outcome among all study subjects. I estimated the prevalence of outcomes overall, and across care settings and provider specialty groups. All analyses including provider specialty groups were only performed for the subgroup of subjects who had surgical procedures (i.e., had either surgical care or surgical plus emergency care), while analyses including care setting were performed for the entire study population. I used unadjusted and covariate adjusted logistic regression models to estimate the association of care setting and provider specialty with study outcomes. I presented odds ratios with 95% confidence intervals (CIs) for all associations assessed. I considered an association to be of potential clinical importance if the odds ratio was at least 1.5 and its CI did not cross the null value. Absolute adjusted prevalence of the outcomes across settings was also presented.

I conducted multiple sensitivity analyses to assess the associations using alternative selection criteria for the population by only including subjects with no recorded history of cancer diagnoses, and another by including only those with a prescription opioid fill that occurred ≤2 days from the emergency department visit. I also assessed the association between provider specialty and study outcomes using an alternative approach to measuring specialty, where I substituted the specialty category of general practice with the second listed specialty when it was a surgical specialty. Finally, I re-ran analyses using alternative thresholds for the outcomes, namely >3 days' supply, >14 days' supply for long days' supply, and ≥50 MME/day for high-dose. I performed all data analyses for Objective 2 using Stata version 15.[1]

3.5.2 Analysis for Objective 3

To describe study population characteristics and characteristics of filled prescriptions, continuous variables were summarized using means with standard deviations when normally distributed and medians with interquartile ranges when skewed. Categorical variables were summarized using frequencies and percentages. I described the overall risk of prolonged opioid use by calculating the proportion of subjects who met the prolonged opioid use definition.

I used regression analysis to estimate unadjusted and covariate-adjusted associations between days' supply (continuous), average daily dose (continuous), opioid type (long- versus short-acting), and prolonged opioid use. I centered both variables at their median values in the model to reduce multicollinearity and improve interpretation of results, as daily dose and days' supply cannot take a value of zero in the included sample. The odds ratio for days' supply was then interpreted as the increment in odds of prolonged use at the median value of daily dose, instead of at the implausible value of zero dose. Similarly, the odds ratio for daily dose was interpreted as the increment in odds of prolonged use at the median value of days' supply. To present the overall association between days' supply, daily dose, and prolonged use, I presented the change in risk of prolonged use that was associated with a one day increase in days' supply and 10 MME/day increase in dose of the first filled prescription. I presented the increase in risk associated with other thresholds for days' supply and daily dose in Appendix 5-C (Chapter 5). Similar to Objective 2, I considered an association to be of potential clinical importance when the odds ratio size was ≥1.5 and the CI did not cross the null value of 1.

I tested for interaction effects between dose and days' supply by including an interaction term in the multivariable model, considering it significant at the level of P =

0.05. The size of the interaction term odds ratio does not provide much information about the nature of the interaction. Therefore, to understand the nature of the interaction, I estimated adjusted predicted probabilities of prolonged opioid use (i.e., absolute risk) with 95% CIs for 20 MME increments of dose values from 10 MME/day to 150 MME/day at three different days' supply values: 3, 7, and 14 days. In this estimation, all other covariates were set at their mean values. I determined differences in absolute risk for the same daily dose across the selected days' supply values. I also tested, at each days' supply value selected, whether the slope of the association between daily dose and prolonged opioid use differed from zero (i.e., indicating that the risk of prolonged use was not constant with increasing level of daily dose) and whether the slope for 7 days and 14 days differed significantly from the slope for 3 days.

To check the robustness of findings across various scenarios, I conducted eight sensitivity analyses. In the first four, I re-ran the analyses for alternative subgroups: the subgroup that had a surgical procedure (whether or not emergency care was also delivered), a second subgroup that had emergency care only, a third subgroup without cancer diagnoses in the previous year, and a fourth subgroup with no additional procedures during the follow-up period, as additional procedures may have been separate indications for prescription opioid use during follow-up. In another three analyses, I used alternative definitions for prolonged use, as described in the Objective 3 variables section 3.4.2 above. In the last sensitivity analysis, I used an alternative approach to assess the interaction between daily dose and days' supply. In this analysis, instead of adding an interaction term to the multivariable analysis model, I categorized dose into a binary variable (≥90 MME/day or <90 MME/day) and categorized days' supply into ≤3 days, 4

to 7 days, or >7 days. I then assessed the association between filling a prescription that was ≥90 MME/day across the three strata for days' supply, adjusting for all covariates described above. All data analyses for Objective 3 were performed using Stata version 15. [1]

3.6 References

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3.7 Appendices

Appendix 3-A Opioid DINs used to identify study cohort.
(*Courtesy of BACK Program and Hayden et al. 2021:* Hayden JA, Ellis J, Asbridge M, Ogilvie R, Merdad R, Grant DAG, et al. Prolonged opioid use among opioid-naive individuals after prescription for nonspecific low back pain in the emergency department. Pain. 2021;162(3):740-8.)

Morphine			
Morphine LP Epidural 0.5mg/mL Inj	02021056	M-Eslon ER 15mg Cap	02177749
Morphine LP Epidural 1mg/mL Inj	02021048	Kadian 20mg Cap	02184435
Morphine Sulfate 1mg/mL Inj	01980696	MS-IR 20mg Tab	02014238
Doloral 1mg/mL Syr	00614491	Statex 20mg Supp	00596965
Statex 1mg/mL Syr	00591467	Statex 20mg/mL Drops	00621935
Morphine Sulfate 2mg/mL Inj	02242484	Statex 25mg Tab	00594636
Morphine Sulfate 2mg/mL Inj	01964437	Morphine SR 30mg Tab	02350890
Morphine Sulfate 5mg/mL Inj	01964429	Novo-Morphine SR 30mg Tab	02302772
MS-IR 5mg Tab	02014203	Sandoz Morphine SR 30mg Tab	02244791
Statex 5mg Tab	00594652	MS Contin 30mg Tab	02014297
Statex 5mg/mL Syr	00591475	M-Eslon ER 30mg Cap	02019949
Morphine Sulfate 10mg/mL Inj	00392588	MS-IR 30mg Tab	02014254
Kadian 10mg Cap	02242163	Statex 30mg Supp	00639389
M-Eslon ER 10mg Cap	02019930	Morphine HP 50mg/mL Inj	00617288
MS-IR 10mg Tab	02014211	Kadian 50mg Cap	02184443
Statex 10mg Supp	00632201	Statex 50mg Tab	00675962
Statex 10mg Tab	00594644	Statex 50mg/mL Drops	00705799
Morphine SR 15mg Tab	02350815	Morphine SR 60mg Tab	02350912
Novo-Morphine SR 15mg Tab	02302764	Novo-Morphine SR 60mg Tab	02302780
Sandoz Morphine SR 15mg Tab	02244790	Sandoz Morphine SR 60mg Tab	02244792
MS Contin 15mg Tab	02015439	MS Contin 60mg Tab	02014300
Morphine Sulfate 15mg/mL Inj	00392561	M-Eslon ER 60mg Cap	02019957
Novo-Morphine SR 100mg Tab	02302799	Novo-Morphine SR 200mg Tab	02302802
MS Contin 100mg Tab	02014319	MS Contin 200mg Tab	02014327
Kadian 100mg Cap	02184451	M-Eslon ER 200mg Cap	02177757
M-Eslon ER 100mg Cap	02019965		
Hydromorphone			
pms-Hydromorphone 1mg/mL Oral Sol	01916386	Apo-Hydromorphone 8mg Tab	02364158
Dilaudid 1mg/mL Oral Sol	00786535	pms-Hydromorphone 8mg Tab	00885428
Apo-Hydromorphone 1mg Tab	02364115	Teva-Hydromorphone 8mg Tab	02319446
pms-Hydromorphone 1mg Tab	00885444	Dilaudid 8mg Tab	00786543
Teva-Hydromorphone 1mg Tab	02319403	Jurnista 8mg Tab	02337274

Dilaudid 1mg Tab	00705438	Hydromorph Contin 9mg Cap	02359510
Hydromorphone 2mg/mL Inj	02145901	Hydromorphone HP 10mg/mL Inj	02145928
Dilaudid 2mg/mL Inj	00627100	Dilaudid HP 10mg/mL Inj	00622133
Apo-Hydromorphone 2mg Tab	02364123	Hydromorph Contin 12mg Cap	02125366
pms-Hydromorphone 2mg Tab	00885436	Jurnista 16mg Tab	02337282
Teva-Hydromorphone 2mg Tab	02319411	Hydromorph Contin 18mg Cap	02243562
Dilaudid 2mg Tab	00125083	Hydromorphone HP 20mg/mL Inj	02145936
Hydromorph Contin 3mg Cap	02125323	Hydromorph Contin 24mg Cap	02125382
Apo-Hydromorphone 4mg Tab	02364131	Hydromorph Contin 30mg Cap	02125390
pms-Hydromorphone 4mg Tab	00885401	Jurnista 32mg Tab	02337290
Teva-Hydromorphone 4mg Tab	02319438	Hydromorphone HP 50mg/mL Inj	02146126
Dilaudid 4mg Tab	00125121	Hydromorph Contin 4.5mg Cap	02359502
Jurnista 4mg Tab	02337266	Hydromorph Contin 6mg Cap	02125331
Oxycodone			
Targin 2.5/5mg Tab	02387425	Targin 10/20mg Tab	02339617
pms-Oxycodone 5mg Tab	02319977	OxyNeo 15mg Tab	02372533
Oxy-IR 5mg Tab	02231934	pms-Oxycodone 20mg Tab	02319993
pms-Oxycodone 5mg Tab	02319977	Oxy-IR 20mg Tab	02240132
Supeudol 5mg Tab	00789739	pms-Oxycodone 20mg Tab	02319993
Targin 5/10mg Tab	02339609	Supeudol 20mg Tab	02262983
pms-Oxycodone 10mg Tab	02319985	OxyNeo 20mg Tab	02372797
Oxy-IR 10mg Tab	02240131	Supeudol 20mg Supp	00392472
pms-Oxycodone 10mg Tab	02319985	Targin 20/40mg Tab	02339625
Supeudol 10mg Tab	00443948	OxyNeo 30mg Tab	02372541
OxyNeo 10mg Tab	02372525	OxyNeo 40mg Tab	02372568
Supeudol 10mg Supp	00392480	OxyNeo 60mg Tab	02372576
		OxyNeo 80mg Tab	02372584
Codeine, combination excluding psycholeptics			
ratio-Emtec Tab	00608882	Atasol 30 Tab	00293512
ratio-Lenoltec #3 Tab	00653276	Tylenol #3 Tab	02163926
ratio-Lenoltec #4 Tab	00621463	Tylenol #4 Tab	02163918
Meperidine			
Meperidine 50mg/mL Inj	00725765	Meperidine 75mg/mL Inj	00725757
Demerol 50mg Tab	02138018	Meperidine 100mg/mL Inj	00725749
Fentanyl			
CO Fentanyl 12mcg/hr Patch	02386844	RAN-Fentanyl MTX 75mcg/hr Patch	02330148
MYLAN-Fentanyl Matrix 12mcg/hr Patch	02396696	Sandoz Fentanyl 75mcg/hr Patch	02327155
pms-Fentanyl MTX 12mcg/hr Patch	02341379	Teva-Fentanyl 75mcg/hr Patch	02282976
RAN-Fentanyl MTX 12mcg/hr Patch	02330105	Duragesic MAT 75mcg/hr Patch	02275848
Sandoz Fentanyl 12mcg/hr Patch	02327112	Apo-Fentanyl 100mcg/hr	02314665

		Patch	
Teva-Fentanyl 12mcg/hr Patch	02311925	CO Fentanyl 100mcg/hr Patch	02386895
Apo-Fentanyl 25mcg/hr Patch	02314630	MYLAN-Fentanyl Matrix 100mcg/hr Patch	02396742
CO Fentanyl 25mcg/hr Patch	02386852	pms-Fentanyl 100mcg/hr Patch	02341417
MYLAN-Fentanyl Matrix 25mcg/hr Patch	02396718	RAN-Fentanyl MTX 100mcg/hr Patch	02330156
pms-Fentanyl MTX 25mcg/hr Patch	02341387	Sandoz Fentanyl 100mcg/hr Patch	02327163
RAN-Fentanyl MTX 25mcg/hr Patch	02330113	Teva-Fentanyl 100mcg/hr Patch	02282984
Sandoz Fentanyl 25mcg/hr Patch	02327120	Duragesic MAT 100mcg/hr Patch	02275856
Teva-Fentanyl 25mcg/hr Patch	02282941	Abstral 100mcg SL Tab	02364174
Duragesic MAT 25mcg/hr Patch	02275813	Abstral 200mcg SL Tab	02364182
Apo-Fentanyl 50mcg/hr Patch	02314649	Abstral 300mcg SL Tab	02364190
CO Fentanyl 50mcg/hr Patch	02386879	Abstral 400mcg SL Tab	02364204
MYLAN-Fentanyl Matrix 50mcg/hr Patch	02396726	Abstral 600mcg SL Tab	02364212
pms-Fentanyl 50mcg/hr Patch	02341395	Fentanyl Citrate 50mcg/mL Inj	00888346
RAN-Fentanyl MTX 50mcg/hr Patch	02330121	Fentanyl Citrate 50mcg/mL Inj	02240434
Sandoz Fentanyl 50mcg/hr Patch	02327147	CO Fentanyl 75mcg/hr Patch	02386887
Teva-Fentanyl 50mcg/hr Patch	02282968	MYLAN-Fentanyl Matrix 75mcg/hr Patch	02396734
Duragesic MAT 50mcg/hr Patch	02275821	pms-Fentanyl 75mcg/hr Patch	02341409
Apo-Fentanyl 75mcg/hr Patch	02314657		
Sufentanil			
Sufentanil Citrate 50mcg/mL Inj	02244147	Sufentanil Citrate 50mcg/mL Inj	02442213
Ketamine			
Ketamine 10mg/mL Inj	02246795	Ketamine 50mg/mL Inj	02246796
Ketalar 10mg/mL Inj	00224391	Ketalar 50mg/mL Inj	00224405
Dextropropoxyphene			
Talwin 30mg/mL Inj	02241976	Talwin 50mg Tab	02137984
Buprenorphine*			
Butrans-5 5mcg/hr Patch *	02341174	Butrans-20 20mcg/hr Patch *	02341220
Butrans-10 10mcg/hr Patch *	02341212		
Butorphanol			
Apo-Butorphanol Nasal Sp	02242504		
Tramadol			
Apo-Tramadol 50mg Tab	02426153	Ralivia 200mg Tab	02299208
Ultram 50mg Tab	02349469	Zytram XL 200mg Tab	02286432
Taro-Tramadol ER 100mg Tab	02450429	Taro-Tramadol ER 300mg Tab	02450445
Tridural 100mg Tab	02296381	Tridural 300mg Tab	02296411
Ralivia 100mg Tab	02299194	Ralivia 300mg Tab	02299216
Zytram XL 150mg Tab	02286424	Zytram XL 300mg Tab	02286440

Taro-Tramadol ER 200mg Tab	02450437	Zytram XL 400mg Tab	02286459
Tridural 200mg Tab	02296403		
Tramadol (combinations)			
Apo-Tramadol/Acet 37.5/325mg Tab	02336790	pms-Tramadol/Acet 37.5/325mg Tab	02401657
Auro-Tramadol/Acetaminop 37.5mg/325mg Tab	02439050	RAN-Tramadol/Acet 37.5/325mg Tab	02388197
CO Tramadol/Acet 37.5/325mg Tab	02383209	Teva-Tramadol/Acetaminophen 37.5/325mg Tab	02347180
Jamp-Acet-Tramadol 325/37.5mg Tab	02388308	Tramadol/Acet 37.5/325mg Tab	02426803
Mar-Tramadol/Acet 37.5/325mg Tab	02388324	Tramadol/Acet 37.5/325mg Tab	02429969
MINT-Tramadol/Acet 37.5/325mg Tab	02389800	Tramacet 37.5/325mg Tab	02264846
Methadone*			
Metadol 1mg Tab	02247698	Metadol 10mg Tab	02247700
Metadol 1mg/mL O/L	02247694	Metadol 10mg/mL O/L	02241377
Metadol 5mg Tab	02247699	Metadol 25mg Tab	02247701
Additional DINs (Not identified in formulary)			
282 Mep Tab			00002238646
282 Tablets			00002234510
292 Tab			00000219843
292 Tab 375mg			00002238645
Ac & C Tab 8mg			00000180041
Acetaminophen 300mg With Caffeine & Codeine Cap			00002154234
Acetaminophen Caffeine & 8mg Cod.Phos. Tab			00001997688
Acetaminophen Compound Caplets With Codeine			00002028174
Acetaminophen Compound Tab With Codeine			00002025337
Acetaminophen W Caffeine & Codeine Tab 8mg			00000706221
Acetaminophen With Codeine - Caplet 300mg			00002143933
Acetaminophen, Caffeine & Codeine Tab 8mg			00002251914
Acetazone Forte C-8 Tab			00000834319
Acet-Codeine Tab 30mg			00001999648
Act Buprenorphine/Naloxone Tab 2mg/.5mg			00002453908
Act Buprenorphine/Naloxone Tab 8mg/2mg			00002453916
Act Oxycodone Cr Extended Release Tab 10mg			00002394189
Act Oxycodone Cr Extended Release Tab 20mg			00002394197
Act Oxycodone Cr Extended Release Tab 40mg			00002394200
Act Oxycodone Cr Extended Release Tab 5mg			00002394170
Act Oxycodone Cr Extended Release Tab 80mg			00002394219
Apo-Oxycodone Cr Extended Release Tab 10mg			00002366754
Apo-Oxycodone Cr Extended Release Tab 15mg			00002394766
Apo-Oxycodone Cr Extended Release Tab 20mg			00002366762
Apo-Oxycodone Cr Extended Release Tab 30mg			00002394774
Apo-Oxycodone Cr Extended Release Tab 40mg			00002306530
Apo-Oxycodone Cr Extended Release Tab 5mg			00002366746
Apo-Oxycodone Cr Extended Release Tab 60mg			00002394782
Apo-Oxycodone Cr Extended Release Tab 80mg			00002366789
Apo-Oxycodone/Acet Tab 5/325mg			00002324628
Atasol-15 Tab 300mg			00000293504
Atasol-8 Tab			00000293490
Belbuca Soluble Film 150mcg/Dose*			00002465248

Belbuca Soluble Film 75mcg/Dose*	00002465221
Butrans 15 Patch 15mcg/Hour*	00002450771
Calmylin Codeine Syrup 10mg/5ml**	00002172917
Calmylin Ace Codeine Syrup 10mg/5ml**	00002198630
Calmylin W Codeine Cough Syr 19.8mg/30ml Original**	00000535230
Coactifed (Expectorant) Liq 10mg/5ml**	00000068756
Coactifed Syrup 10mg/5ml**	00000068594
Coactifed Tab 20mg**	00000068608
Codeine Contin Sustained-Release Tab 50mg	00002230302
Codeine Contin Tab 100mg	00002163748
Codeine Contin Tab 150mg	00002163780
Codeine Contin Tab 200mg	00002163799
Codeine Phosphate Liq Inj Usp 30mg/Ml	00000544884
Codeine Phosphate Pdr	00000905518
Codeine Phosphate Syrup 4.7666mg	00000050024
Codeine Powder	00099099975
Codeine Syrup 5mg/Ml	00000093114
Codeine Tab 30mg	00000779466
Codeine Tab 30mg	00000093130
Codeine Tab 30mg	00002009757
Cophylac**	00001987577
Cophylac**	00002224577
Cophylac Dps**	00000116343
Darvon N 100mg Cap	00000261432
Demerol Hcl Tab 50mg	00000033685
Demerol Inj 100mg/Ml Liq	00002242005
Demerol Inj 50mg/Ml Liq	00002139022
Dilaudid Hp Plus Inj 20mg/Ml Liq	00002146118
Dilaudid Sup 3mg	00000125105
Dilaudid Tab 2mg	00000290572
Dilaudid Tab 4mg	00000290602
Dimetane Expectorant C Syr 10mg/5ml**	00002244079
Dimetane Expectorant C Syr 10mg/5ml**	00001934716
Dimetane Expectorant Dc Syr**	00001934708
Dimetane Expectorant Dc Syrup 20mg/Ml**	00002244080
Dimetapp C Syr**	00002244078
Doloral 5 Sirop 5mg/Ml	00000614505
Duragesic Mat Patch 12mcg/Hr	00002334186
Duragesic Patch 12mcg/Hour	00002280345
Duragesic Patch Srd 100mcg/Hr	00001937413
Duragesic Patch Srd 25mcg/Hr	00001937383
Duragesic Patch Srd 50mcg/Hr	00001937391
Duragesic Patch Srd 75mcg/Hr	00001937405
Endocet Tab 325/5 Mg	00000574384
Endocet Tab 5/325 Mg	00001916548
Fentanyl Citrate Inj Liq	00002384124
Fentanyl Citrate Inj Liq 50mcg/Ml	00002385406
Fentanyl Compound	00000994025
Fentanyl Patch Srd 50mcg/Hr	00002304139
Fentora Tab 100mcg	00002408007
Fentora Tab 200mcg	00002408015
Fentora Tab 400mcg	00002408023
Fentora Tab 600mcg	00002408031

Fiorinal C 1/2 Cap	00000176206
Fiorinal C 1/4 Cap	00000176192
Hycodan Syrup 1mg/Ml**	00001916580
Hycodan Tab 5mg**	00001916599
Hydromorph Ir Tab 2mg	00002245703
Hydromorph Ir Tab 4mg	00002245704
Hydromorphone Compound	00000994006
Hydromorphone Hcl Liq 10mg	00002460610
Hydromorphone Hcl Liq Inj 2mg/Ml	00002460602
Hydromorphone Hcl Usp High Potency 10mg	00002382636
Hydromorphone Hp Forte Inj 100mg/Ml Liq	00002244797
Hydromorphone Powder	00099099980
Lomotil Tab 2.5mg**	00000399345
Lomotil Tab 2.5mg**	00000036323
M.O.S. "1" Syr 1mg/Ml	00000486582
M.O.S. "10" Tab 10mg	00000690198
M.O.S. "20" Conc Liq 20mg/Ml	00000632481
M.O.S. "20" Tab 20mg	00000690201
M.O.S. "5" Syr 5mg/Ml	00000514217
M.O.S. "60" Tab 60mg	00000690244
M.O.S. Sr Tab 30mg	00000776181
M.O.S. Sr Tab 60mg	00000776203
M.O.S. Sulphate Tab 10mg	00002009765
M.O.S. Sulphate Tab 25mg	00002009749
M.O.S. Sulphate Tab 50mg	00002009706
M.O.S. Sulphate Tab 5mg	00002009773
Meperidine Hcl Liq Inj 100mg/Ml	00000497479
Mersyndol Tab	00002047667
M-Eslon Ir Cap 10mg	00002320428
M-Eslon Ir Cap 30mg	00002320444
Metadol-D Oral 10mg/Ml	00002244290
Methadone Injectable	00000994901
Methadone O/L (Mg)	00099099993
Methadone Pwd (Compound) 1mg	00000999734
Methadose Sol'n 10mg/Ml	00002394596
Methadose Unflavored Sol'n 10mg/Ml	00002394618
Methoxacet C 1/8 Caplets	00002236872
Methoxisal C 1/4	00001966367
Methoxisal C1/2 Caplets	00001966375
Morphine Hp 25 Liq Inj 25mg/Ml	00000676411
Morphine Hydrochloride Compound	00000994009
Morphine Liq Inj 10mg/Ml	00002382997
Morphine Powder	00099099986
Morphine Sr Tab 100mg	00002350920
Morphine Sr Tab 200mg	00002350947
Morphine Sulfate Liq Inj 10mg/Ml	00000850322
Morphine Sulfate Liq Inj 10mg/Ml	00000497355
Morphine Sulfate Liq Inj 5mg/Ml Usp Iv	00000649619
Morphine Sulphate Pws	00000999955
Muscle & Back Pain Relief - 8 Tab	00002242180
Mylan-Buprenorphine/Naloxone Tab 2mg/.5mg*	00002408090
Mylan-Buprenorphine/Naloxone Tab 8mg/2mg*	00002408104
Nf Cough Syrup With Codeine**	00002099748

Novahistex Dh Adult Syrup**	00002049481
Novahistine Dh Children Syr**	00002049473
Nucynta Cr Tab 100mg	00002360381
Nucynta Cr Tab 150mg	00002360403
Nucynta Cr Tab 200mg	00002360411
Nucynta Cr Tab 50mg	00002360373
Nucynta Extended Release Tab 100mg	00002415585
Nucynta Extended Release Tab 150mg	00002415593
Nucynta Extended Release Tab 200mg	00002415607
Nucynta Extended Release Tab 250mg	00002415615
Nucynta Extended Release Tab 50mg	00002415577
Nucynta Ir Tab 100mg	00002378299
Nucynta Ir Tab 50mg	00002378272
Nucynta Ir Tab 75mg	00002378280
Onsolis Soluble Film 200mcg	00002350661
Onsolis Soluble Film 400mcg	00002350688
Onsolis Soluble Film 600mcg	00002350696
Onsolis Soluble Film 800mcg	00002350718
Opium & Belladona Sup	00001923463
Oxycodone Tab 5mg	00002325950
Oxycodone/Acet Tab 5/325mg	00002361361
Oxycodone-Acet Tab 5/325mg	00002327171
Oxycontin Extended Release Tab 15mg	00002323192
Oxycontin Extended Release Tab 30mg	00002323206
Oxycontin Extended Release Tab 60mg	00002323214
Oxycontin Srt 10mg	00002202441
Oxycontin Srt 20mg	00002202468
Oxycontin Srt 40mg	00002202476
Oxycontin Srt 5mg	00002258129
Oxycontin Srt 80mg	00002202484
Pat-Fentanyl Mat Patch 12mcg/Hour	00002376768
Percocet Demi Tab 2.5mg/325mg	00001916491
Percocet Tab 5/325 Mg	00000389641
Percocet Tab 5mg/325 Mg	00001916475
Percodan 325/5mg Tab	00001916572
Pharmasave Cough Syr	00000690074
Phl-Hydromorphone Tab 2mg	00002249928
Pms-Acetaminophen W Codeine Elixir 32mg	00000816027
Pms-Buprenorphine/Naloxone Sublingual Tab 8/2mg*	00002424878
Pms-Buprenorphine/Naloxone Sublingual Tab 2/.5mg*	00002424851
Pms-Butorphanol Nasal Spray 10mg/Ml	00002244508
Pms-Codeine 15mg Tab	00002243978
Pms-Codeine 30mg Tab	00002243979
Pms-Hydrocodone Syr 1mg/Ml	00002324253
Pms-Hydromorphone Supp 3mg	00001916394
Pms-Morphine Sulfate Srt 15mg	00002245284
Pms-Morphine Sulfate Srt 30mg	00002245285
Pms-Morphine Sulfate Srt 60mg	00002245286
Pms-Morphine Sulfate Srt 100mg	00002245287
Pms-Morphine Sulfate Srt 200 Mg	00002245288
Pms-Opium And Belladona Sup	00000815349
Pms-Oxycodone Cr Extended Release Tab 10mg	00002309882
Pms-Oxycodone Cr Extended Release Tab 20mg	00002309890

Pms-Oxycodone Cr Extended Release Tab 40mg	00002309904
Pms-Oxycodone Cr Extended Release Tab 80mg	00002309912
Pms-Oxycodone-Acetaminophen 325/5mg	00002245758
Ran-Fentanyl Transdermal 100mcg/Hour	00002249448
Ran-Fentanyl Transdermal 25mcg/Hour	00002249391
Ran-Fentanyl Transdermal 50mcg/Hour	00002249413
Ran-Fentanyl Transdermal 75mcg/Hour	00002249421
Ratio-Codeine Syrup 5mg/Ml	00000779474
Ratio-Codeine Tab 15mg	00000593435
Ratio-Codeine Tab 30mg	00000593451
Ratio-Cotridin 10mg/5ml	00002169126
Ratio-Lenoltec #1 Tab	00000653233
Ratio-Lenoltec #2 Tab 300mg	00000653241
Ratio-Morphine Syrup 10mg/Ml	00000690783
Ratio-Morphine Syrup 1mg/Ml	00000607762
Ratio-Morphine Syrup 5mg/Ml	00000607770
Ratio-Morphine Syrup Conc 20mg/Ml	00000690791
Ratio-Oxycocet Tab 5/325 Mg	00000608165
Ratio-Oxycodan Tab 5mg/325mg	00000608157
Ratio-Tecnal C 1/2 Cap	00000608181
Ratio-Tecnal-C 1/4 Cap	00000608203
Robaxacet-8 Tab	00001934767
Robaxisal C-1/2 Tab	00001934791
Robaxisal C-1/4 Tab	00001934783
Robitussin A-C Syr 10mg/5ml**	00001934740
Sandoz Fentanyl Patch 37mcg/H	00002327139
Sandoz Opium & Belladonna Sup	00001901869
Sandoz Oxycodone/Acetaminophen Tab 5mg/325mg	00002307898
Statex Supp 5mg	00000632228
Suboxone Sublingual Tab 12/3mg*	00002468085
Suboxone Sublingual Tab 2/.5mg*	00002295695
Suboxone Sublingual Tab 8/2mg*	00002295709
Tussionex Srt	00001916963
Tussionex Suspension Srs	00001916971
Tylenol No.1 Caplets	00002181061
Tylenol No.2 Tab 300mg	00002163934
Tylenol No.3 Tab	00000425389
Tylenol WITH CODEINE ELIXIR 32MG	00002163942

* Buprenorphine and methadone formulations used to treat opioid use disorder excluded from base cohort
** Cough and anti-diarrhea medications excluded from base cohort

Appendix 3-B: Surgical procedures and emergency department visit codes. Any individual with a documented procedure code from the list below or a code for an ED visit occurring on or up to 14 days prior to an opioid fill was eligible for inclusion in the cohort.

Data source	Variables used	Description	Categorization	Code category/ range
MSI Physicians' Billings	ccpcat (CCP Category)	Category of the procedure for which the individual was billed	(Bone Grafts)	BOGR
			(Casts and Splints)	CASP
			(Dislocation)	DISL
			(Major Fracture)	MAFR
			(Major Surgery)	MASG
			(Minor Fracture)	MIFR
			(Minor Surgery)	MISG
CIHI DAD	Intervention code 11/02 (CCI code)	Category for the intervention which the individual had received	(Obstetrical)	OBST
			Therapeutic Interventions on the Eye and Ocular Adnexa	1CC - 1CZ
			Therapeutic Interventions on the Ear and Mastoid (process)	1DA - 1DZ
			Therapeutic Interventions on the Orocraniofacial Region	1EA - 1FX
			Therapeutic Interventions on the Respiratory System	1GA - 1GZ
			Therapeutic Interventions on the Cardiovascular System	1HA - 1LZ
			Therapeutic Interventions on the Lymphatic System	1MA - 1MZ
			Therapeutic Interventions on the Digestive and Hepatobiliary Tracts and Other Sites within the Abdominal Cavity NEC	1NA - 1OZ
			Therapeutic Interventions on the Genitourinary System	1PB - 1RZ
			Therapeutic Interventions on the Musculoskeletal System	1SA - 1WZ
			Therapeutic Interventions on the Skin, Subcutaneous Tissue and Breast	1YA - 1YZ
			Antepartum Interventions	5AB - 5CA
			Interventions During Labour and Delivery	5LB - 5MD
NACRS	ED visit (leaving ED), derived from [registration_date]	A date representing leaving the ED	Yes vs. No	NA

Appendix 3-C: Data and variables requested from HDNS. This table was included in the data request form presented to HDNS in November, 2019 to request the study dataset(s) for the research team to access. The dataset(s) are accessed on a secure remote portal for analysis.

For Objectives 2 and 3 of this thesis, I requested data linkage across the following seven databases: (1) The Drug Information System (DIS), (2) Medical Services Insurance (MSI) Physician's Billings (3) Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD), (4) CIHI National Ambulatory Care Reporting System (NACRS), (5) Licensed Provider Registry, (6) Insured Patient Registry (MASTER), and (7) Vital Statistics (VITAL). See Table 3.1 for a description of each database. Study subjects were initially identified from the DIS database (i.e., by having filled an opioid prescription during the study period), and then filtered by applying the inclusion and exclusion criteria, as described below, using information from the DIS, MSI Physicians' Billings, CIHI DAD, and NACRS databases. Data on study variables were obtained from the same four databases as well as the: (1) Licensed Provider Registry for prescriber variables, (2) Insured Patient Registry for sociodemographic variables, and (3) Vital Statistics for death during follow-up.

Two datasets were created. The first dataset included information about the study cohort. The second dataset included information about opioid prescriptions that were filled by subjects included in the cohort during the study follow-up period. I merged the two datasets for data cleaning, reorganization according to the study objectives, and analyses using the statistical analysis and data science software Stata version 15.[130]

Data requested from HDNS

#	Source Dataset	Variable (*identify whether HDNS or derived variable*)	Level of Identification	Time Span	Why is this element required in the analysis?	Why is this level of identification required?
	1. LINKING VARIABLES					
1	MASTER, DIS, VITAL, DAD, NACRS	Encrypted HCN (msi)	To be replaced by study ID	Jan. 26, 2017 – March 31st 2019 [or latest available date]	To link individuals across databases	Linking variable
2	DIS, LPR	Unique ID for each prescriber derived from [DIS_PROVIDER_ID] in DIS and [doctor] in LPR	To be replaced by provider study ID	Jan. 26, 2017 – March 31st 2019 [or latest available date]	To link providers across datasets	Linking variable
	2. SAMPLE SELECTION VARIABLES					
3	DIS	Opioid (from list of DINs in Appendix 5) was filled within study period. Derived from [PICKUP_DATE]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest available date]	To select study sample	To exclude subject if =0
4	DIS	ID of each opioid filled within study period [DIS_PRESCRIPTION_ID]	To be replaced by prescription study ID	Jan. 26, 2017 – March 31st 2019 [or latest available date]	For HDNS internal use only to extract data on included prescriptions	Cannot be further collapsed
5	LPR	Surgeon prescribed the opioid. Derived from [dspecial] using the following codes: (CASG, GNSG, NUSG, OBGY, ORTH, OTOL, PLAS, RADI, THSG, UROL, VASG)	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest available date]	To select study sample	To determine whether subject meets the acute pain indication definition

6	LPR	Dentist prescribed the opioid. Derived from [dspecial] using the following codes: (DENT, ENDO, ODON, ORAL, PEDO, PERI, PROS)	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
7	LPR	Emergency medicine physician prescribed the opioid. Derived from [dspecial] using the following codes: (EMMD)	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
8	NACRS	Patient had ED visit within study period. Derived from [ED_visit_indicator and Registration_date]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
9	NACRS	ED visit (leaving ED) date. Derived from [registration_date]	Date (DD/MM/YYYY)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
10	NACRS, DIS	ED visit (leaving ED) occurred on or up to 14 days before an opioid fill (if applicable). Derived from DIS [PICKUP_DATE] and NACRS [registration_date].	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
11	MSI	Any CCP category (from list in Appendix 5) occurred within study period. Derived from [ccpcat] and [dxdate]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition

12	MSI	Date of CCP code [dxdate]	Date (DD/MM/YYYY)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
13	MSI, DIS	CCP code occurred on or up to 14 days before an opioid fill. Derived from MSI [dxdate] and DIS [PICKUP_DATE]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
14	CIHI DAD	Any CCI category (from list in Appendix 5) occurred within study period. Derived from CIHI DAD [Procedure code 1-20]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
15	CIHI DAD	Date of CCI code. Derived from CIHI DAD [pdate1-pdate20]	Date (DD/MM/YYYY)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
16	CIHI DAD, DIS	CCI code occurred on or up to 14 days before opioid fill. Derived from CIHI DAD [pdate1-pdate20] and DIS [PICKUP_DATE]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To select study sample	To determine whether subject meets the acute pain indication definition
17	DIS	The prescription ID of the opioid fill meeting the acute pain indication definition (or earliest one if multiple) [DIS_PRESCRIPTION_ID] = Index prescription fill	Prescription ID	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	For HDNS internal use only to identify index prescription and linkage	Prescription linkage variable

18	DIS	Date of index prescription fill (identified in variable # 18) for each unique study ID [PICKUP_DATE] (only one per Study ID)	Date (DD/MM/YYYY)	Jan. 26, 2017 – March 31st 2019 [or latest available date]	1. To select study sample (age/enrollment status on day of index prescription fill) 2. To determine index prescription factors for objective 1 and 2 and 'date of entry' into the study for objective 2	Cannot be further collapsed
19	MASTER and DIS	Age on day of index prescription fill. DERIVED from [PICKUP_DATE] in DIS and [dob] in MASTER	Age in years at time of index prescription fill	Jan. 26, 2017 – March 31st 2019 [or latest available date]	1. To select study sample 2. To describe baseline characteristics and analyze as a risk factor	1. To exclude if <18 years) 2. To retain information and explore shape of relationship between age and the outcome graphically
20	MASTER and DIS	Enrollment ended within the 365 days preceding the date of index prescription fill (without re-enrollment prior to index fill). Derived [PICKUP_DATE] identified in variable # 18 and MASTER [todate] (most recent)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest available date]	To select study sample	To exclude subject if =1
21	MASTER and DIS	There was a lapse in enrollment within 365 days preceding the date of index prescription fill. Derived [PICKUP_DATE] identified in variable # 18 and MASTER [todate] (all 'todate' variables within 365 days)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest available date]	For sensitivity analysis	Cannot be further collapsed
22	DIS	Opioid naive 90: One or more opioids filled (from list of DINs provided in Appendix 5) in the 90 days preceding the index opioid fill date. Derived from [DRUG_CODE and PICKUP_DATE]	Binary variable (0=no, 1=yes)	Oct. 28, 2016 – March 31st 2019 [or latest available date]	To select study sample	To exclude if =1

23	DIS	Opioid naive 180: One or more opioids filled (from list of DINs provided in Appendix 5) in the 180 days preceding the index opioid fill. Derived from [DRUG_CODE and PICKUP_DATE] ONLY derive if subject had index fill date = April 26, 2017 or after	Binary variable (0=no, 1=yes)	Oct. 28, 2016 – March 31st 2019 [or latest availabl e date]	For sensitivity analysis; to test impact of opioid naivety (90 days) definition	Cannot be further collapsed
	3. PATIENT VARIABLES					
24	MASTE R	Sex [SEX]	Binary variable (0=male, 1=female)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze as a risk factor	Cannot be further collapsed
25	MASTE R and DIS	Enrollment ended on or before March 31, 2019 [or latest available date] but *after* date of index prescription fill. Derived from the [PICKUP_DATE] identified in variable # 18 and MASTER [todate]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To determine eligibility for inclusion in objective 2	Cannot be further collapsed
26	MASTE R	Date of discontinuation of enrollment after index prescription fill (if applicable) [todate]	Date (DD/MM/YYY Y)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct survival analysis	Exact date is needed to estimate censoring time
27	VITAL	Death occurred after date of index prescription fill. Derived [PICKUP_DATE] identified in variable # 18 and VITAL [dod]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct survival analysis	Cannot be further collapsed

28	**VITAL**	Date of death (if applicable) derived from VITAL [dod]	Date (DD/MM/YYYY)	Jan. 26, 2017 – March 31st 2019 [or latest available date]	To conduct survival analysis	Exact date is needed because survival time is counted in days in the analysis (i.e. for each subject, the number of days from the index prescription fill to death (if applicable) is included in the survival analysis.
29	NACRS	ED visit [ED Visit Indicator]	Binary variable (0= arranged day surgery or clinic visit taking place in the ED, 1= an ED visit)	Jan. 26, 2017 – March 31st 2019 [or latest available date]	To consider excluding non-ED visits (by researcher)	Cannot be further collapsed
30	MSI, CIHI DAD	12-m history of depression. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest available date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
31	MSI, CIHI DAD	12-m history of anxiety disorder. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest available date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
32	MSI, CIHI DAD	12-m history of alcohol abuse. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest available date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
33	MSI, CIHI DAD	12-m history of drug and substance abuse. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest available date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed

34	MSI, CIHI DAD	12-m history of tobacco use. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
35	MSI, CIHI DAD	12-m history of low back pain. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
36	MSI, CIHI DAD	12-m history of headache/migraine. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
37	MSI, CIHI DAD	12-m history of arthritis/joint pain or neck pain. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
38	MSI, CIHI DAD	12-m history of fibromyalgia. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
39	MSI, CIHI DAD	12-m history of neuropathic pain. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed

40	MSI, CIHI DAD	12-m history of other chronic pain. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
41	MSI, CIHI DAD	12-m history of cancer. Derived from MSI [dxcode 1-3] and CIHI DAD [dxcode 1-25] by identifying any single ICD code from those listed in Table 2 (Appendix 5)	Binary variable (0=no, 1=yes)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To describe baseline characteristics and analyze co-morbidity as a risk factor	Cannot be further collapsed
42	MSI	CCP category associated with index prescription fill (if applicable) [ccpcat]	Category	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To identify most likely indication for opioid prescription	Cannot be further collapsed without compromising important information
43	MSI	The specialty under which the provider billed for the service encounter (the CCP identified from [ccpcat] above (variable # 42). [bspecial]	Specialty(s) listed	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To capture all provider specialties	To compare to LPR variable to determine most likely specialty of opioid prescribing provider
44	MSI	Treatment location [location] of the CCP identified from [ccpcat] above (variable # 42).	Categorical variable CCNT (Correctional Centre) HMHC (Home Hospital Care) HOME (Patient's Home) HOSP (Hospital) NRHM (Nursing Home) OFFC (Physician's Office) OTHR (Other)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To capture where the procedure occurred	To compare to LPR variable to determine most likely specialty of opioid prescribing provider
45	MSI	One or more of the CCP categories (from pre-specified list in Appendix 5) occurred *after* the index prescription fill	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct sensitivity analysis for objective 2	Cannot be further collapsed

46	MSI	Procedure date for the earliest CCP that occurred after index prescription fill (if applicable). Derived from [dxdate]	Date (DD/MM/YYYY)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct sensitivity analysis for objective 2	Cannot be further collapsed
47	CIHI DAD	CCI category associated with index prescription fill (if applicable) [procedure code 1-20]	Category	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To identify most likely indication for opioid prescription	Cannot be further collapsed without compromising important information
48	CIHI DAD	One or more CCI category (from pre-specified list) occurred *after* the index prescription fill. Derived from [Procedure date 1-20]	Binary variable (0=no, 1=yes)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct sensitivity analysis for objective 2	Cannot be further collapsed
49	CIHI DAD	Procedure date for the earliest CCI that occurred after index prescription fill (if applicable). Derived from [Procedure date 1-20]	Date (DD/MM/YYYY)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct sensitivity analysis for objective 2	Cannot be further collapsed
	4. PRESCRIPTION VARIABLES					
50	DIS	Date of opioid fill that occurred during study period [PICKUP_DATE]	Date the prescription was picked up (DD/MM/YYYY) for the index prescription and each subsequent fill during the study follow up period	Jan 26, 2017 - Mar 31, 2019 [or latest availabl e date]	To calculate: 1. Time to opioid cessation, 2. Follow up time, 3. Year of filing of index prescription within the study period	Cannot be further collapsed (must include exact date)
51	DIS	Fill number. Derived	Categorical variable (0= index fill, 1= 1st subsequent fill in follow up; 2= 2nd subsequent fill in follow up …)	Oct 28, 2016- Mar 31, 2019 [or latest availabl e date]	To calculate time to opioid cessation in objective 2.	Cannot be further collapsed.

52	DIS and LPR	Unique ID for each prescriber derived from [DIS_provider_ID] in DIS and [doctor] in LPR (Variable # 2)	Unique ID	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	To account for clustering by prescriber in the multilevel modeling	Cannot be further collapsed.
53	DIS	Opioid Code (from list in Appendix 5) [DRUG_CODE]	Drug Identification Number	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	1.Necessary to confirm eligibility of subject for inclusion in the cohort. 2. Necessary to describe types of opioids prescribed. 2.Necessary to measure the *high-risk prescription* variables that are based on opioid type.	Exact drug code needed to determine type and to calculate Morphine Milligram Equivalent dose
54	DIS	Opioid name [DRUG_NAME]	Name of opioid filled	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate dose in MME	Exact drug code needed to determine type and to calculate Morphine Milligram Equivalent dose
55	DIS	Route [ROUTE_CODE]	Route of administration	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate dose in MME	Cannot be further collapsed.
56	DIS	Dispensed quantity [DISPENSED_QTY]	Medication dispensed quantity as continuous variable	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate dose in MME	Cannot be further collapsed.
57	DIS	Dispensed quantity unit [DISPENSED_QTY_UNIT]	Categorical variable: unit (U, cup_us, foz_br, qt_br, tbs_us, tsp_us, iU, mg, ml, mol, u)	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate average daily dose in MME	Cannot be further collapsed.
58	DIS	Drug strength [DRUG_STRENGTH]	Continuous variable	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate average daily dose in MME	Cannot be further collapsed.

59	DIS	Drug strength unit [DRUG_STRENGTH_UNIT]	Categorical variable: unit (Amb a 1 unit, BA unit, Elisa unit/mL, IR, SPF, SQ-HDM, Billion cell, Billion unit, gram, gram/dose, gram/gram, gram/mL, mEq, mEq/mL, mL, mcg, mcg/1, hour, mcg/24 hour, mcg/gram, mcg/mL, mcg/spray, mg, mg/1 hour, mg/24 hour, mg/3 day, mg/dose, mg/gram, mg/mL, mg/spray, mmol/mL, pollen unit/mL, tub. Unit/mL, unit, unit/gram, unit/mL, unit/spray)	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate average daily dose in MME	Cannot be further collapsed.
60	DIS	Expected use duration (time) [EXPECTED_USE_TIME]	Continuous variable	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate days' supply and average daily dose in MME	Cannot be further collapsed.
61	DIS	Expected use unit [EXPECTED_USE_TIME_UNI T]	Categorical variable: unit (days, hours, minutes)	Oct 28, 2016-Mar 31, 2019 [or latest availabl e date]	Study 2 and 3 to calculate days' supply and average daily dose in MME	Cannot be further collapsed.
	5. PRESCRIBER VARIABLES					
62	LPR	Specialties associated with the prescriber [dspecial]	List of specialties associated with the provider	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To stratify average prescription characteristics and prevalence of high-risk prescribing by prescriber specialty	Needed to map to specialty groups after assessing distribution of specialties

63	LPR	Years since graduation. Derived from [gradyear]	Binary variable for years since graduation at the time of index prescription fill (0= [< 10 years],1=[≥ 10 years])	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To stratify average prescription characteristics and prevalence of high-risk prescribing by years since graduation	Cannot be further collapsed.
64	LPR	Place of graduation. Derived from [location]	Binary variable (0=Canada, 1=Other).	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To stratify average prescription characteristics and prevalence of high-risk prescribing by place of graduation	Cannot be further collapsed.
	6. ADDITIONAL VARIABLES					
65	MASTE R	Date of death (if applicable) [tstat]	Date (DD/MM/YYY Y)	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct survival analysis	Exact date is needed because survival time is counted in days in the analysis (i.e. for each subject, the number of days from the index prescription fill to death (if applicable) is included in the survival analysis.
66	CIHI DAD	Discharge date	Date (DD/MM/YYY Y)	Jan. 26, 2016 – March 31st 2019 [or latest availabl e date]	To identify requested co-morbidities	Exact date is needed to determine whether the comorbidity occurred in the 12 months preceding the index prescription.
67	NACRS	For subjects who met inclusion criteria based on having an ED visit on or up to 14 days before the index opioid fill: Number of days from ED visit to index prescription fill	Continuous variables (range 0-14) with 0=same day as ED visit	Jan. 26, 2017 – March 31st 2019 [or latest availabl e date]	To conduct sensitivity analysis for objective 2	Exact number of days needed

HDNS: Health Data Nova Scotia; ED: Emergency Department; DIS: Drug Information System dataset; MSI: MSI Physicians' Billings database, DAD: Canadian Institute of Health Informatics Discharge Abstract Database, NACRS: CIHI National Ambulatory Care Reporting Systems; LPR: Licensed Provider Registry database; VITAL: Vital statistics; MASTER: Insured Patient Registry.

Appendix 3-D: ICD diagnostic codes used to measure 12-month history of physical and mental health co-morbidities. For each of the included health conditions, we defined history of conditions as present if at least one of the corresponding diagnostic codes was found in MSI Physicians' Billings (ICD-9-CM) or CIHI DAD (ICD-10-CA) databases in the 12 months prior to the index fill. Studies previously applying variable definition are cited.

Variable	ICD-9-CM codes*	ICD-9-CM code labels	ICD-10-CA codes*	ICD-10-CA code labels
History of depression	296.2, 296.3, 296.5, 300.4, 309, 311 (MCHP, Himelhoch 2004)	296.2 Major depressive disorder, single episode 296.3, Major depressive disorder, recurrent episode 296.5, Bipolar I disorder, most recent episode (or recurrent) depressed 300.4, Dysthymic disorder 309, Adjustment reaction 311 Depressive disorder NEC	F20.4, F31.3–F31.5, F32, F33, F34.1, F41.2, F43.2 (MCHP)	F20.4, Post-schizophrenic depression F31.3–F31.5, Bipolar affective disorder, current episode mild or moderate depression; current episode severe depression without psychotic symptoms; current episode severe depression with psychotic symptoms F32, Depressive episode F33, Recurrent depressive disorder F34.1, Dysthymia F41.2, Mixed anxiety and depressive disorder F43.2, Adjustment disorders
History of anxiety disorder	300 (ICD Manual)	Anxiety, dissociative and somatoform disorders	F32.0, F40, F41, F42, F44, F45.0, F45.1, F45.2, F48, F68.0, F99 (Martens 2015)	F32.0, Mild depressive episode F40, Phobic anxiety disorders F41, Other anxiety disorders F42, Obsessive-compulsive disorder F44, Dissociative [conversion] disorders F45.0, Somatization disorder F45.1, Undifferentiated somatoform disorder F45.2, Hypochondriacal disorder F48, Other neurotic disorders F68.0, Other disorders of adult personality and behavior F99 Mental disorder, not otherwise specified
History of alcohol abuse	265.2, 291.1–291.3, 291.5, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1–571.3, 980, V11.3 (MCHP)	265.2 Pellagra, 291.1–291.3 Alcoholic amnestic disorder, alcohol persist dementia, alcohol-induced psychotic disorder with hallucinations 291.5 Alcohol-induced psychotic disorder with delusions 291.8, Other specified alcohol-induced mental disorders 291.9, Unspecified alcohol-induced mental disorders 303.0, Acute alcoholic intoxication 303.9, Other and unspecified alcohol dependence	E52, F10, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51, Z50.2, Z71.4, Z72.1 (MCHP), Z86.40 (ICD Manual)	History of Alcohol Abuse E52, Niacin deficiency [pellagra] F10, Mental and behavioural disorders due to use of alcohol G62.1, Alcoholic polyneuropathy I42.6, Alcoholic cardiomyopathy K29.2, Alcoholic gastritis K70.0, Alcoholic fatty liver K70.3, Alcohol cirrhosis of liver K70.9, Alcoholic liver disease, unspecified T51, Toxic effect of alcohol Z50.2, Alcohol rehabilitation Z71.4, Alcohol abuse counselling and surveillance Z72.1, Alcohol use Z86.40 Personal history of alcohol abuse

		305.0, Alcohol abuse 357.5, Alcoholic polyneuropathy 425.5, Alcoholic cardiomyopathy 535.3, Alcoholic gastritis 571.0, Alcoholic fatty liver 571.1–571.3, Acute alcoholic hepatitis; alcoholic cirrhosis of liver; alcoholic liver damage, unspecified 980, Toxic effect of alcohol V11.3 Personal history of alcoholism		
History of drug and substance abuse	292, 304, 305.2–305.9, V65.42 (MCHP)	292, Drug-induced mental disorders 304, Drug dependence 305.2–305.9, Cannabis abuse; hallucinogen abuse; sedative, hypnotic or anxiolytic abuse; opioid abuse; cocaine abuse; amphetamine or related acting sympathomimetic abuse; antidepressant type abuse; other, mixed, or unspecified drug abuse V65.42Counseling on substance use and abuse	F16, F18, F19, Z71.5, Z72.2 (MCHP), Z50.3, Z86.41, Z86.48 (ICD Manual)	F16, Mental and behavioural disorders due to use of hallucinogens F18, Mental and behavioural disorders due to use of volatile solvents F19, Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances Z71.5, Drug abuse counselling and surveillance Z72.2, Drug use Z50.3, Drug rehabilitation Z86.41, Personal history of drug abuse Z86.48, Personal history of other psychoactive substance abuse
History of tobacco abuse	305.1, V15.82 (ICD Manual)	305.1, Tobacco use disorder V15.82 History of tobacco use	F17, Z71.6, Z72.0, Z86.42, T65.2 (ICD Manual)	F17, Mental and behavioural disorders due to use of tobacco Z71.6, Tobacco abuse counselling Z72.0, Tobacco use Z86.42, Personal history of tobacco abuse T65.2 (ICD Manual) Toxic effect of tobacco and nicotine
History of low back pain	721.3x – 721.9x, 722.2x, 722.30, 722.70, 722.80, 722.90, 722.32, 722.72, 722.82, 722.92, 722.73, 722.83, 722.93, 724.xx, 737.1, 737.3, 738.4, 738.5, 739.2, 739.3, 739.4, 756.10, 756.11, 756.12, 756. 13, 756.19, 805.4, 805.8, 839.2, 839.42, 846, 846.0, 847.1, 847.3, 847.2, 847.9 (Shah 2017)	721.3x – 721.9x, Lumbosacral spondylosis without myelopathy; thoracic or lumbar spondylosis with myelopathy; 722.2x, Displacement of intervertebral disc, site unspecified, without myelopathy 722.30, Schmorl's nodes, unspecified region 722.70, Intervertebral disc disorder with myelopathy, unspecified region	M51.3, M54.3, M54.4, M54.5, M54.8, M54.9, (HQ Ontario)	M51.3, Other specified intervertebral disc degeneration M54.3, Sciatica M54.4, Lumbago with sciatica M54.5, Low back pain M54.8, Other dorsalgia M54.9, Dorsalgia, unspecified site

	722.80, Postlaminectomy syndrome, unspecified region 722.90, Other and unspecified disc disorder, unspecified region 722.32, Schmorl's nodes, lumbar region 722.72, Intervertebral disc disorder with myelopathy, thoracic region 722.82, Postlaminectomy syndrome, thoracic region 722.92, Other and unspecified disc disorder, thoracic region 722.73, Intervertebral disc disorder with myelopathy, lumbar region 722.83, Postlaminectomy syndrome, lumbar region 722.93, Other and unspecified disc disorder, lumbar region 724.xx, Other and unspecified disorders of back 737.1, Kyphosis (acquired) 737.3, Kyphoscoliosis and scoliosis 738.4, Acquired spondylolisthesis 738.5, Other acquired deformity of back or spine 739.2, Nonallopathic lesions, thoracic region 739.3, Nonallopathic lesions, lumbar region 739.4, Nonallopathic lesions, sacral region 756.10, Anomaly of spine NOS 756.11, Lumbosacral spondylolysis 756.12, Spondylolisthesis 756.13, Absence of vertebra, congenital 756.19, Other anomalies of spine 805.4, Closed fracture of lumbar vertebra without

		mention of spinal cord injury 805.8, Closed fracture of unspecified vertebral column without mention of spinal cord injury 839.2, Dislocation; thoracic and lumbar vertebra, closed 839.42, Closed dislocation, sacrum 846, Sprains and strains of sacroiliac region 846.0, Sprain lumbosacral 847.1, Sprain thoracic region 847.3, Sprain of sacrum 847.2, Sprain lumbar region 847.9, Sprain of back NOS		
History of headache/migraine	>=346 AND <347 OR 307.81 (Shah 2017)	>=346 AND <347 Migraine; 307.81 tension headache	G43-G44, R51 (ICD Manual)	G43-G44, Migraine, Other headache syndromes R51 Headache
History of arthritis/joint pain or neck pain	>=710 AND <720 OR >=725 AND <740 (Shah 2017) 721.0x, 721.1x, 722.0x, 722.31, 722.71, 722.81, 722.91, 723.XX, 839.0, 839.1, 847. 0 (Shah 2017)	>=710 AND <720 (710 to 719) Arthropathies and related disorder OR >=725 AND <740 (725 to 729) Rheumatism, excluding the back (730 to 739) Osteopathies, chondropathies, and acquired musculoskeletal deformities (Shah 2017) 721.0x, Cervical spondylosis 721.1x, Cervical spondylosis with myelopathy 722.0x, Displacement of cervical intervertebral disc without myelopathy 722.31, Schmorl's nodes, thoracic region 722.71, Intervertebral disc disorder with myelopathy, cervical region 722.81, Postlaminectomy syndrome, cervical region	M05 – M14 (excluding M08 and M09), M15-M25, M30-M36, M40-M53 (excluding M51.3) (ICD Manual)	M05 – M14 (excluding M08 and M09), Seropositive rheumatoid arthritis, other rheumatoid arthritis, psoriatic and enteropathic arthropathies, gout, other crystal arthropathies, other specific arthropathies, other arthritis, arthropathies in other diseases classified elsewhere M15-M25 (M15-M19 Arthrosis and M20-M25 Other joint disorders): Polyarthrosis; coxarthrosis; gonarthrosis; arthrosis of first carpometacarpal joint; other arthrosis; acquired deformities of fingers and toes; other acquired deformities of limbs; disorders of patella; internal derangement of knee; other specific joint derangement; other joint disorders; not elsewhere classified M30-M36 (Systemic connective tissue disorders): Polyarteritis nodosa and related conditions; other necrotizing vasculopathies; systemic lupus erythematosus; dermatopolymyositis, systemic sclerosis, other systemic involvement of connective tissue, systemic disorders of connective tissue in diseases classified elsewhere M40-M53 (excluding M51.3): Kyphosis and lordosis; scoliosis; spinal osteochondrosis; other deforming dorsopathies; ankylosing spondylitis; other spondylopathies; spondylosis; other spondylopathies;

		722.91, Other and unspecified disc disorder, cervical region 723.XX, Other disorders of cervical region 839.0, Dislocation; cervical vertebra, closed 839.1, Dislocation; cervical vertebra, open 847.0 Sprain of neck (Shah 2017)		spondylopathies in diseases classified elsewhere; cervial disc disorders; other intervertebral disc disorders; other dorsopathies; not elsewhere classified
History of fibromyalgia	729.1x (Shah 2017)	Myalgia with myositis NOS	M79.7 (ICD Manual)	M79.7 Fibromyalgia
History of neuropathic pain	357, 337.0, 356.0, 356.2, 356.4, 356.9, 357.2, 357.3, 531.3, 723.4, 727.2 (Shah 2017)	357 Inflammatory and toxic neuropathy 337.0, Idiopathic peripheral autonomic neuropathy 356.0, Hereditary peripheral neuropathy 356.2, Hereditary sensory neuropathy 356.4, Idiopathic progressive polyneuropathy 356.9, Unspecified hereditary and idiopathic peripheral neuropathy 357.2, Polyneuropathy in diabetes 357.3, Polyneuropathy in malignant disease 531.3, Acute gastric ulcer; without mention of hemorrhage or perforation 723.4, Brachial neuritis or radiculitis NOS 727.2 Specific bursitides often of occupational origin	G62.8, G62.9, G63.2, G63.3-G63.8, G90.0, G99.0, K25.4-K25.9, K26.4-K26.9, K27.4-K27.9, K28.4-K28.9, M54.1 (ICD Manual)	G62.8, Other specified polyneuropathies G62.9, Polyneuropathy, unspecified G63.2, Diabetic polyneuropathy G63.3-G63.8, Polyneuropathy in other endocrine and metabolic diseases; polyneuropathy in nutritional deficiency; polyneuropathy in systemic connective tissue disorders; polyneuropathy in other musculoskeletal disorders; polyneuropathy in other diseases classified elsewhere. G90.0, Idiopathic peripheral autonomic neuropathy G99.0, Other disorders of nervous system in diseases classified elsewhere K25.4-K25.9, Gastric ulcer, chronic or unspecified with haemorrhage; gastric ulcer, chronic or unspecified with perforation; gastric ulcer, chronic or unspecified with both haemorrhage and perforation; gastric ulcer, chronic without haemorrhage or perforation; gastric ulcer, unspecified as acute or chronic, without haemorrhage or perforation K26.4-K26.9, Duodenal ulcer, chronic or unspecified with haemorrhage; duodenal ulcer, chronic or unspecified with perforation; duodenal ulcer, chronic or unspecified with both haemorrhage and perforation; duodenal ulcer, chronic without haemorrhage or perforation; duodenal ulcer, unspecified as acute or chronic, without haemorrhage or perforation K27.4-K27.9, Peptic ulcer, chronic or unspecified with haemorrhage; peptic ulcer, chronic or unspecified with perforation; peptic ulcer, chronic or unspecified with both haemorrhage and perforation; peptic ulcer, chronic without haemorrhage or perforation; peptic

				ulcer, unspecified as acute or chronic, without haemorrhage or perforation K28.4-K28.9, Gastrojejunal ulcer, chronic or unspecified with haemorrhage; gastrojejunal ulcer, chronic or unspecified with perforation; gastrojejunal ulcer, chronic or unspecified with both haemorrhage and perforation; gastrojejunal ulcer, chronic without haemorrhage or perforation; gastrojejunal ulcer, unspecified as acute or chronic, without haemorrhage or perforation M54.1 Radiculopathy
History of cancer	All ICD-9-CM malignant neoplasm codes except non-melanoma skin cancer	-	All ICD-10-CA malignant neoplasm codes except non-melanoma skin cancer	-

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4 Chapter Four: Patterns of opioid prescribing to opioid-naive patients after surgical and emergency care: a population-based cross-sectional study using linked administrative databases in Nova Scotia (2017 - 2019)

4.1 Note to reader

In this chapter, I summarize the patterns of opioid prescribing to opioid-naive adults in Nova Scotia who filled opioid prescriptions within 14 days of surgical and/or emergency care. I also present evidence showing that a proportion of patients receive first prescriptions in excess of seven days' supply and 90 MME/day, and show how these patterns of prescribing vary across clinical settings and, for those in surgical care, across provider specialties.

4.2 Manuscript information

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Student contribution to the manuscript: Roah Merdad conceived the research question with input from her co-supervisors, Drs. Jill Hayden and Mark Asbridge. Roah designed the study, managed data, conducted and interpreted all analyses with input from co-supervisors and other co-authors. She wrote the manuscript draft and revised all drafts.

4.3 Manuscript

4.3.1 Abstract

Objective: We describe prescribing patterns to opioid-naive patients who filled opioid prescriptions following surgical or emergency care, and assess variation in prescribing >7days' supply or ≥90MME/day across settings and provider specialties.

Methods: We conducted a cross-sectional population-based study of opioid-naive adults who filled opioid prescriptions in community pharmacies within 14 days of receiving surgical or emergency care in Nova Scotia, Canada. We employed linked administrative databases to summarize prescribing patterns and estimate prevalence of prescriptions >7 days' supply, ≥90 MME/day, or for long-acting opioids. We assessed association of care setting and provider specialty with these outcomes, adjusting for patient characteristics and procedure type.

Results: Among 36,716 subjects, median days' supply was 3 days (IQR2-5), median daily dose was 50 morphine milligram equivalents(MME)/day (IQR30-75), and hydromorphone (50.0%) and codeine (26.4%) were the most filled formulations. Prescriptions >7days' supply and ≥90MME/day were filled by 10.9% and 20.2%. Adjusting for patient characteristics, the emergency care group had double the odds of filling >7days' supply (aOR 2.13, 95%CI 1.99-2.28), and 66% lower odds of filling ≥90MME/day (aOR 0.34, 95%CI 0.31–0.37) compared to surgical care. In the surgical care group, adjusting for patient characteristics and procedure type, potentially important differences across provider specialties were observed.

Conclusion: The majority of filled prescriptions were for short-acting opioids, below 7days' supply, and below 90MME/day. Variations across settings and specialties were observed for prescriptions above these values. We recommend that future studies explore whether differences in patients' clinical needs or other factors, such as prescribing cultures, explain these variations.

4.3.2 Introduction

Background

Each year, thousands of patients in Canada interact with the healthcare system for acute pain requiring emergency care, or receive surgical care that is associated with significant pain postoperatively.[1-3] Opioids are frequently prescribed in these settings, with recent evidence finding that over three-quarters of patients who had surgery between 2013 and 2016 in Canada filled opioids within seven days of discharge[4], and over one-third of patients who visited an emergency department in Nova Scotia for non-specific low-back pain between 2009 and 2015 were discharged with an opioid prescription.[5] Many patients who receive opioids for acute pain are opioid-naive at the time.[6,7] Opioid-naivety is frequently defined as no documented opioid use in the six to twelve months preceding a new fill. In the year 2018, 8.1% of the Canadian population started opioids while opioid-naive.[6]

Certain patterns of prescribing have been shown to be associated with higher risk of opioid-related harms in opioid-naive populations. Prescriptions that are longer in duration, higher in dose, or for long-acting opioids may be associated with higher risk of prolonged use[8,9], misuse [10], and overdose[11]. Canadian quality monitoring initiatives for opioid prescribing to patients with acute pain, and opioid prescribing guidelines for

postoperative and injury-related pain in the United States recommend that, when opioids are deemed necessary to treat acute pain in opioid-naive populations, prescriptions are written for short-acting formulations in the lowest effective dose for the shortest duration possible.[12-14] In general, these guidelines indicate that three days are often sufficient and exceeding seven days' supply is rarely needed.

Although thresholds for prescribing are only meant to guide care for the majority of, but not all, patients, and first-prescriptions that are written in excess of one week or in high-dose may be necessary for some opioid-naive patients for whom recovery duration is expected to be long or who are expected to have severe pain, evidence suggests that physicians frequently prescribe opioids in excess of patient need. A systematic review on quantity of opioids consumed after surgery, and a Canadian study that followed patients after emergency department visits found that patients who filled opioids used only between one-quarter to one-third of their supply.[15,16] Previous studies have also shown that variations in opioid prescribing patterns are sometimes explained by prescriber – rather than patient – characteristics, including prescriber rank[17,18], specialty[19], and time pressure[20]. A survey of 500 physicians about their choice of pain management in the immediate postoperative period found that previous clinical experiences were the most commonly cited motivation for choice of medication, more so than surgery type, adherence to clinical practice guidelines, or a review of relevant literature.[21]

Importance

Currently, little is known about prescribing patterns to opioid-naive populations in Canada. Few studies described patterns of prescribing to populations with pain regardless of setting or pain acuity[7,11], or for restricted populations in a single setting.[22] Estimating

the prevalence of prescribing in excess of one week or for high-dose or long-acting formulations will contribute to our understanding about safety of prescribing to opioid-naive populations in acute care settings, and potentially about their unique needs. Setting and provider specialty can serve as proxies for common clinical and training experiences among physician groups, and they can be explored as potential determinants of differences in prescribing patterns.

Goals of this study

The objectives of this study are to (1) describe patterns of opioid prescribing to opioid-naive adults who fill opioid prescriptions in community pharmacies after surgical or emergency care in Nova Scotia, Canada; (2) determine the prevalence of filling prescriptions that are >7 days, ≥90 MME/day or for long-acting opioids (primary outcomes), strong opioids, or tramadol (secondary outcomes); and (3) determine whether setting – for all subjects - and provider specialty – for those who had procedures - are associated with these outcomes adjusting for patient characteristics and procedure type.

4.3.3 Methods

Study design and setting: We conducted a cross-sectional, population-based study in the province of Nova Scotia, Canada, using individual-level data linked across the following five routinely collected administrative databases: the provincial Drug Information System (DIS), MSI Physicians' Billings (MSI), and Insured Patient Registry (MASTER) databases; and the national Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), and CIHI National Ambulatory Care Reporting System (NACRS) – (Table 3-1). Databases were linked using unique encoded identifiers at Health Data Nova Scotia, Dalhousie University. A de-identified dataset was made accessible to the

research team - obtaining informed consent was considered impracticable. The study was approved by the Health Sciences Research Ethics Board at Dalhousie University (REB# 2019-4896).

Selection of study population: We included all adults (≥18 years) in the province of Nova Scotia, Canada, who were opioid-naive and filled opioid prescriptions in community pharmacies between April 26, 2017 and March 31, 2019 within 14 days of having procedures or visiting and emergency departments (ED) that report to NACRS. We defined naivety as no prescription opioid fills in 180 days preceding a first fill and no fill for an opioid use disorder medication in the first three subsequent fills, if additional opioid prescriptions were filled by the subject. Using the DIS database, we identified all opioid prescriptions that were filled by adults within the study period, then excluded (a) those that had another opioid fill in the preceding 180 days, (b) fills for opioid formulations treating cough, diarrhea, or opioid use disorder and (c) fills without active insurance in the 12-month look-back period - opioid codes in Appendix 3-A in Chapter 3. After identifying fills of relevance, the DIS database was linked to MSI, CIHI-DAD, and NACRS databases, and those that did not have at least one code for a surgical procedure or ED visit in the 14-day look-back period were excluded, similar to previous studies considering fills up to two weeks to be directly related to the acute pain event.[23,24] (Codes in Appendix 3-B in Chapter 3).

Study variables:

Characteristics of filled prescriptions and study outcomes

The primary outcomes of interest were fills for prescriptions >7 days' supply, fills for prescriptions ≥90 MME/day, and fills for long-acting opioids. Secondary outcomes

were prescription fills for strong opioids and tramadol which are of concern due to potential opioid-related harms [25] and unpredictable metabolism.[26] For each eligible subject, we obtained data from the DIS database about the first single prescription that met inclusion criteria during the study period and set the day of the fill as the subject's index day. For each fill, we obtained data about days' supply as calculated by the pharmacist and documented in the DIS database, quantity, strength, and formulation, which we categorized into codeine, hydromorphone, oxycodone, morphine, tramadol, or other. We also mapped opioids based on form of release (short vs. long-acting), and potency (weak vs. strong). We calculated dose in MME using the formula and conversion factors provided by the Ontario Drug Policy Research Network.[27] For subjects with multiple opioid fills on index day, MME was summed across all filled prescriptions to calculate total MME, and then divided by the number of days of the prescription with the longest days' supply. Long-acting formulations were prioritized in the opioid type variable when both short- and long-acting formulations were filled. See section 3.4.1 in Chapter 3 for details.

Setting of care and specialty of procedure provider (exposures)

Based on identified codes in the 14-day look-back period, each included subject was categorized into one of three mutually exclusive setting groups: surgical care (at least one procedure code with no ED visit codes), emergency care (at least one ED visit code with no procedure codes), or emergency plus surgical care (at least one ED visit and one procedure code). We derived a variable for specialty of procedure provider using data from the MSI database, which we categorized into general surgery, orthopedic surgery, plastic surgery, otolaryngology, urology, other surgical specialties (cardiac-, neuro-,

thoracic-, and vascular-surgery), general practice, and non-surgical non-general practice specialties including medical and interventional radiology specialties. Similar specialties with small frequencies were grouped, as presented.

Patient characteristics and type of procedure (co-variates)

We used data about patient age (continuous, in years) and sex (binary, female or male) on day of opioid filling, and binary variables (yes or no) using inpatient and outpatient ICD-9-CM and ICD-10-CA codes measuring the following conditions in the past 12-months: depression, anxiety, alcohol, drug, and tobacco abuse, low back pain, headache, arthritis, fibromyalgia, neuropathic pain, and cancer, except non-melanoma skin cancer (codes in Appendix 3-D). For subjects who had procedures, we created a procedure type variable categorized into major surgery; minor surgery; fracture, dislocation, or cast; bone grafting; obstetrics; and other (included procedures that were captured in DAD but not MSI database). When a subject received multiple procedures in the 14 day look-back period, we used the procedure that was most proximal to fill date to create the variable. All of these factors were selected as co-variates for adjustment in the analysis based on previous studies indicating that procedure type[21] and perception of patient behaviors and consequences[28] – which may be directly related to history of co-morbidities included - influence physicians' prescribing decisions for pain management.

Statistical analysis: We summarized characteristics of the study sample and filled prescriptions overall and across settings using means with standard deviations and medians with interquartile ranges for continuous variables, and frequencies with percentages for categorical variables. We estimated the prevalence of the outcomes within each care setting and provider specialty group by estimating the proportion of

individuals who had fills > 7 days' supply, ≥ 90MME/day, or were for long-acting opioid formulations, and assessed association of setting and provider specialty with these outcomes using multivariable logistic regression models estimating odds ratios with 95% confidence intervals. Co-variates included for adjustment are mentioned above. We considered an association to be of potential importance when the odds ratio was at least of moderate size (OR ≥ 1.5) and the confidence interval did not cross the null value. We also presented risks of the outcomes across care settings in absolute adjusted values. We conducted sensitivity analyses to test alternative definitions of acute pain (only subjects without history of cancer; only subjects who filled prescription opioids ≤ 2 days from emergency care), alternative categorization of provider specialty (general practice recategorized to second listed surgical specialty), and outcomes defined as > 3 days' supply, > 14 days' supply, and ≥ 50 MME/day. We performed all data management and analyses using Stata version 15.[29]

4.3.4 Results

Characteristics of the study population and filled opioid prescriptions

Of 124,515 adults who filled opioid prescriptions in community pharmacies in Nova Scotia between April 26, 2017 and March 31, 2019, 36,716 subjects were opioid-naive and met the study inclusion criteria (Figure 4-1). Sixty two percent filled a prescription after surgical care, 28% after emergency care, and 10% after emergency plus surgical care. The mean age (±SD) of subjects was 54.2±17.5 years and 55% were female. A past 12-months history of arthritis, joint, or neck pain diagnosis was present in 56.5%, low back pain in 17.6%, anxiety in 15.5%, depression in 10.3%, and cancer in 14.7%. Among 26,445 subjects in the surgical care and emergency plus surgical care groups 77.7% had

major surgery. The most common provider billing specialties in the surgical care and emergency plus surgical care groups were general practice (34.6%), orthopedic surgery (16.3%), general surgery (15.3%), and obstetrics and gynecology (10.2%) –Table 4-1.

Overall, hydromorphone was the most filled opioid (50%; 18,370 subjects), followed by codeine (26.4%), tramadol (8.5%), morphine (7.8%), and oxycodone (7.0%). Median days' supply and dose were 3 days (IQR 2-5) and 50 MME/day (IQR 30 - 75). Less than 1% (251 subjects; 0.7%) filled multiple prescriptions on index day - see Table 4-2 for characteristics across settings.

Prevalence of outcomes and association with setting and specialty of procedure provider

Overall, prescriptions >7 days' supply were filled by 10.9% (n=3,984), ≥90 MME/day by 20.2% (n=7,369), and 0.7% filled prescriptions for long-acting opioids (n=266) – see Table 4-2 and Figure 4-2 for prevalence across settings. Analyses adjusting for patients' age, sex, and 12-month history of depression, anxiety, alcohol abuse, drug abuse, tobacco abuse, low back pain, headache, arthritis, fibromyalgia, neuropathic pain, and cancer, showed that compared to the surgical care group, the emergency care group was 2 times as likely have filled prescriptions >7 days' supply (aOR 2.13, 95% 1.98 - 2.29; absolute adjusted risk 87.1/1000 in surgical care and 166/1000 in emergency care) but less likely have filled ≥90MME/day (aOR 0.34, 95% CI 0.31 - 0.37 – absolute adjusted risk 237/1000 in surgical care and 97/1000 in emergency care). Those in the emergency plus surgical care group were less likely to have filled prescriptions >7 days' supply (aOR 0.86, 95% CI 0.75 – 0.99; absolute adjusted risk 76/1000) and slightly more likely to have filled prescriptions ≥90 MME/day (aOR 1.07, 95% CI 0.99 – 1.16; absolute adjusted risk 249/1000) compared to the surgical group -Table 4-3.

Prevalence of filling prescriptions > 7 days' supply and ≥ 90MME/day across specialty groups is presented in Table 4-3 and Figure 4-3. Among subjects in the surgical care and emergency plus surgical care groups (n= 26,445), 15.2% (n= 4,041) had general surgeons for providers. Using this group as reference and after adjusting for patient characteristics and procedure type, subjects in the following specialties had potentially important higher odds of filling prescriptions >7 days' supply: otolaryngology (aOR 4.77, 95% CI 3.79 to 5.99), other surgical specialties including cardiac-, neuro-, thoracic-, and vascular-surgery (aOR 2.52, 95% CI 1.89 to 3.36), general practice (aOR 2.31 95% CI 1.91 to 2.79), and non-surgical non-general practice specialties (aOR 6.66, 95% CI 4.87 to 9.11). Subjects in the following specialties also had potentially important higher odds of filling prescriptions ≥90MME/day compared to general surgery: orthopedic surgery, obstetrics and gynecology, other surgical specialties, and general practice, while the following specialties had lower odds: plastic surgery, otolaryngology, and urology (Table 3).

Prevalence of filling strong opioids and tramadol (secondary outcomes)

Just below two-thirds of the study population filled prescriptions for strong opioids (65.2%), and 8.5% for tramadol (Table 4-2). Adjusted analyses showed that the emergency care group had a potentially important higher odds of filling tramadol compared to surgical care (aOR 1.79, 95% CI 1.66 to 1.94) and other potentially important differences across settings and procedure provider specialty groups were also observed (results in Appendix 4-A).

Sensitivity analyses

The analysis that included only subjects without history of cancer in the past 12 months showed similar results. Analysis that included only subjects who filled their prescription at ≤ 2 days from emergency care showed a weaker association between emergency care and >7 days' supply outcome. Recategorizing those whose provider specialty was general practice to second listed surgical specialty showed stronger associations, particularly with >7 days' supply and long-acting opioids outcomes. Redefining outcomes as >3 days' supply showed weaker associations, and >14 days' supply showed weaker association for otolaryngology, and stronger associations for other surgical, and non-surgical non-general practice specialties (results in Appendix 4-B to 4-D).

4.3.5 Discussion

We found that prescriptions that were filled by previously opioid-naive subjects after surgical and emergency care in Nova Scotia were written, on average, for 3 days (IQR 2 – 5) and 50 MME/day (IQR 30 – 75), and that half of this population filled hydromorphone formulations, while a quarter filled codeine formulations. We also found that one in ten of the study population had prescriptions that exceeded seven days' supply, around one in five exceeded 90 MME/day, while only <1% filled long-acting formulations. We also found that, after accounting for measured patient characteristics, distinct patterns of prescribing were observed. Subjects who received opioids after emergency care were twice as likely to have long days' supply prescriptions but less than half as likely to fill ≥90MME/day compared to those who received surgical care. Furthermore, we found that among those who filled opioids after surgical care, large relative differences in filling long days' supply and high-dose prescriptions existed across

provider specialty groups. Those who filled prescriptions after a procedure that was billed by otolaryngology had the highest likelihood of filling prescriptions longer than one week's supply among the surgical subspecialties, while prescriptions ≥ 90MME/day were most likely to be filled after a procedure that was billed by orthopedic surgery.

Our study findings on differences in prescribing for patients receiving surgical care across provider specialty groups independent of patient characteristics aligns with recent studies of opioid-naive surgical patients from the United States which found variation in opioid prescribing by provider rank and specialty independent of patient factors.[17-19] The observed differences in this study in prescribing long days' supply by setting and provider specialty independent of patient characteristics may reflect differences in likelihood of overprescribing by specialty groups based on practice conventions. Previous studies found that physicians frequently overprescribe opioids in emergency and surgical settings [15,16] in an attempt to ensure patients have sufficient supply 'just in case'. Subsequently, excessive prescribing may occur more frequently in specialties like otolaryngology that perform more minor surgeries and potentially have longer duration to follow-up appointments, and in settings like emergency care where little information about quantity of opioids consumed after an initial prescription is provided to physicians, as feedback seldom occurs. Another explanation for the observed differences could be variation in average length of stay at the hospital following procedures, and subsequently differences in amount of inpatient opioid prescribing that we could not measure or account for in the study. Still, unmeasured confounding by patients' clinical need could explain the observed variation, and this needs to be explored in future studies.

Study limitations must be noted. The definition of opioid-naivety may have missed patients who use illicitly manufactured opioids or acquire prescription opioids through diversion. A study in the United States found that six out of 82 surgical patients who did not use prescription opioids in the past reported using illicitly manufactured opioids.[30] We identified a small number of subjects who filled formulations used to treat opioid use disorder in their first three subsequent fills, considered them likely non-naive, and excluded them. Misclassified subjects could still be present in the study which might explain the observed low-prevalence of long-acting opioid prescriptions. The indicator for ED visits captured only 52% of ED visits in the province of Nova Scotia in 2017-2018.[2] This may have excluded half of eligible subjects in this setting and the prevalence of outcomes for them remains to be estimated. Finally, lack of adjustment in the analysis for other provider characteristics that are associated with prescribing behaviours and may systematically vary across specialties may have led to unmeasured confounding. In the current study, we did not include other provider characteristics in the analysis as data was missing for 24% of included subjects for these variables, and no information about reasons for or patterns of missingness was available. Differences in propensity for long days' supply or high-dose prescribing by provider within each specialty may also exist. Estimating this variation can provider deeper understanding of patterns of prescribing, and accounting for it in the analysis by including a random effects function may provide us with more accurate estimation of the association between specialty and study outcomes.

To assess the study outcomes, we used data from drug claims which do not include information on inpatient prescriptions or prescriptions that were given but never filled. If

those who do fill their prescriptions are more likely to have had high-dose and long days' supply prescriptions compared to those who do not fill them, then we might observe an over-estimation of the prevalence of these outcomes in the study. Finally, co-morbidity measures may have misclassified subjects if they were not yet diagnosed or if they were using prescription medications but did not have corresponding ICD codes documented in included databases during the 12-month look-back period. These situations, in addition to potentially having missed other important confounders, leaves the possibility of residual confounding in the study that may partially or fully explain the differences in prescribing observed here.

Judicious prescribing of opioids for the treatment of acute pain was identified as a priority to combatting the opioid epidemic.[31,32] Recent evidence shows that institutional regulation and policy legislation can effectively drive down excessive prescribing when appropriate.[33,34] Before determining targets for intervention in care settings and specialties, it might be beneficial to explore possible explanations for variation including possible differences in pain severity, expected duration of recovery, inpatient opioid prescribing and use, and practice norms including time to patient follow up visit. Some patients may benefit from higher dose or long days' supply prescriptions, such as those with severe pain requiring adequate analgesia for early mobilization or those with long expected recovery duration. Therefore, it is important to gain more insight for this population before making recommendations to avoid causing undue restriction on prescribing.

In summary, this study found that overall, the majority of opioid prescriptions filled by opioid-naive patients following surgical and emergency care in Nova Scotia

were below 7 days' supply and 90 MME/day. One in ten had a prescriptions that exceeded 7 days' supply, and one in five had a prescriptions ≥90 MME/day. We found variation across settings and provider specialty groups in these outcomes. We recommend exploring drivers of the observed variation and whether these patterns of prescribing are explained by differences in patients' clinical needs or if other factors, such as prescribing cultures, account for these differences.

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Figure 4-1: Study cohort creation flow diagram

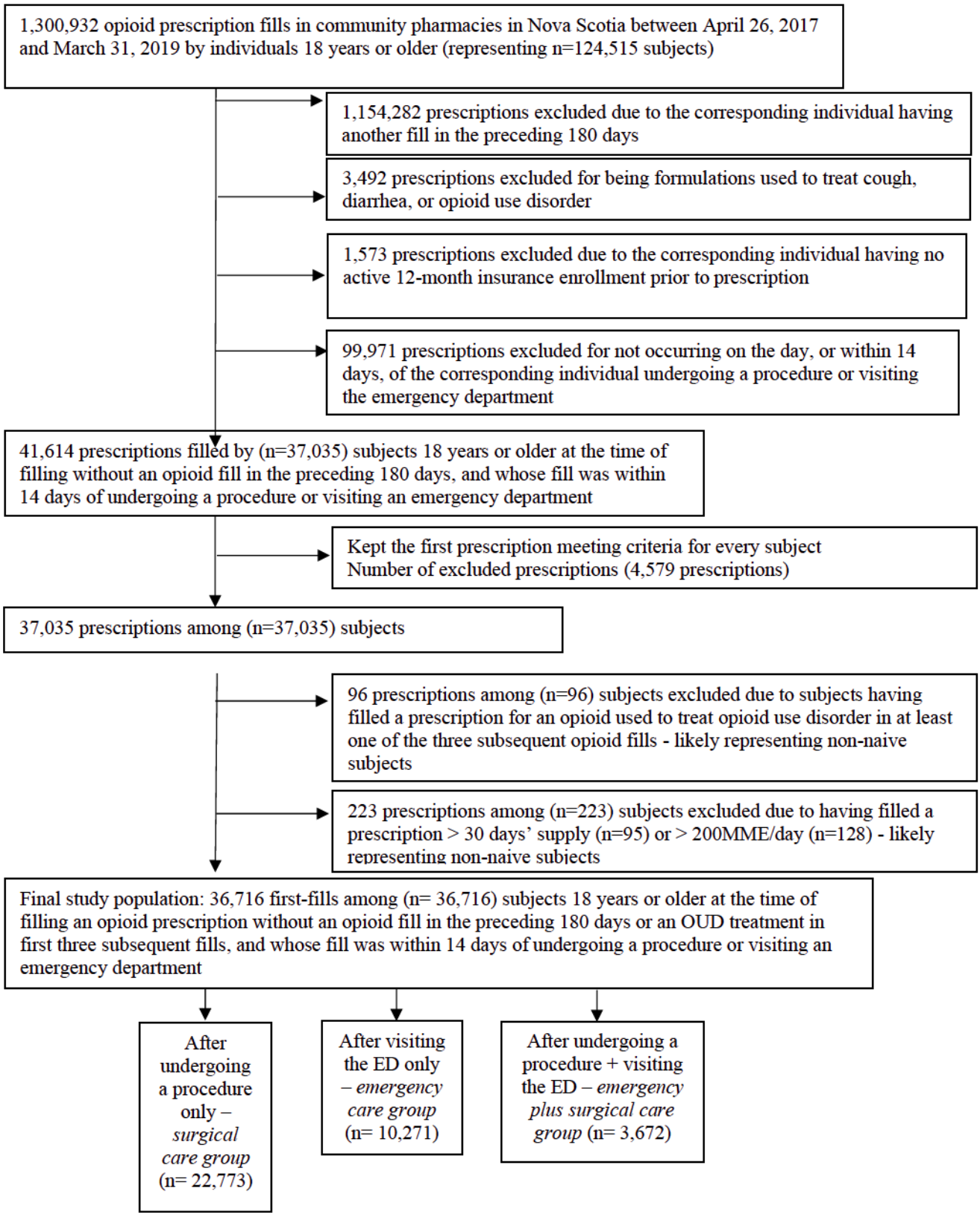
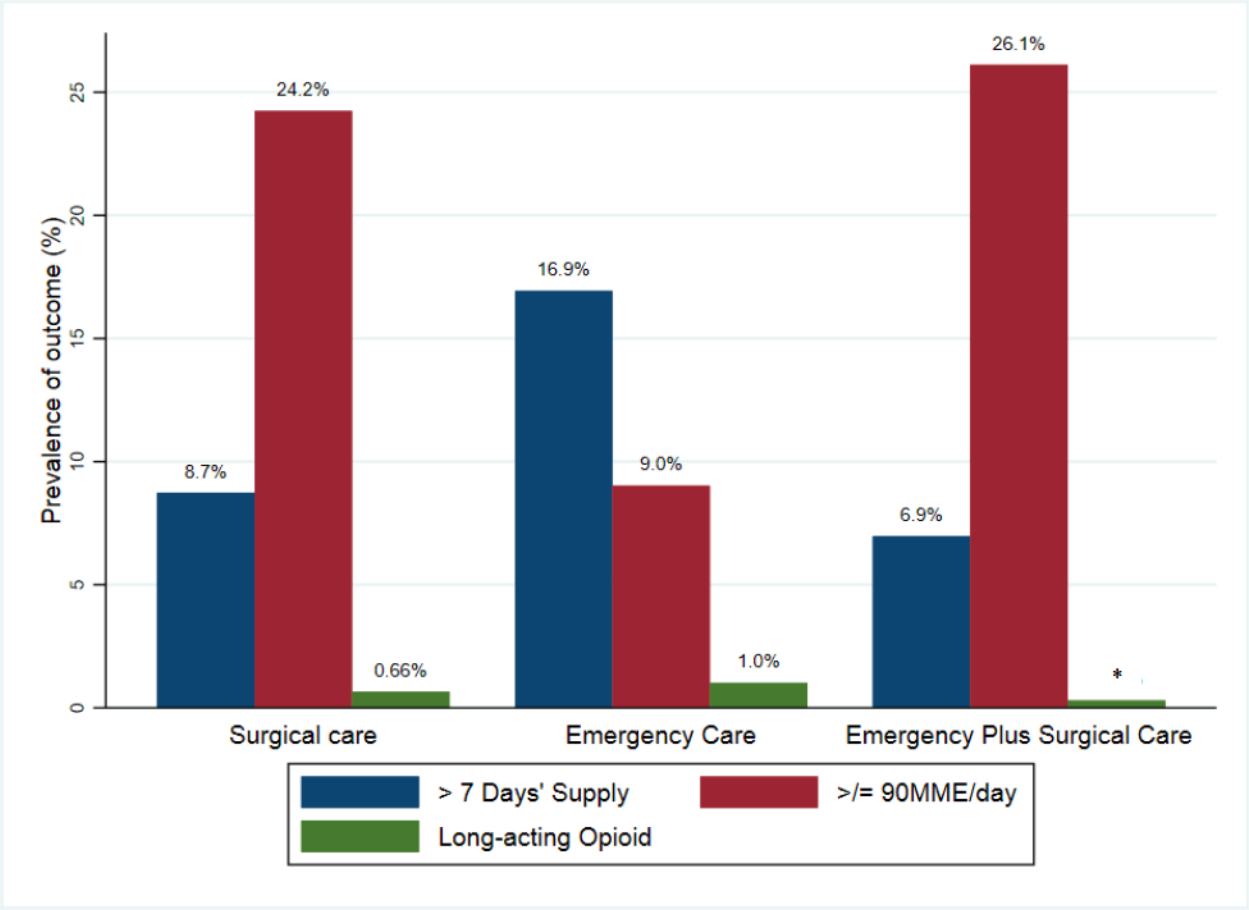


Figure 4-2: Prevalence of filling prescriptions > 7 days' supply, ≥ 90MME/day, and for long-acting opioids across care settings. (n= 36,716)



*Suppressed value (n<5)

Figure 4-3: Prevalence of filling prescriptions > 7 days' supply and ≥ 90MME/day across provider specialty groups for subjects who had procedures (surgical and emergency plus surgical care groups). (n= 26,445)

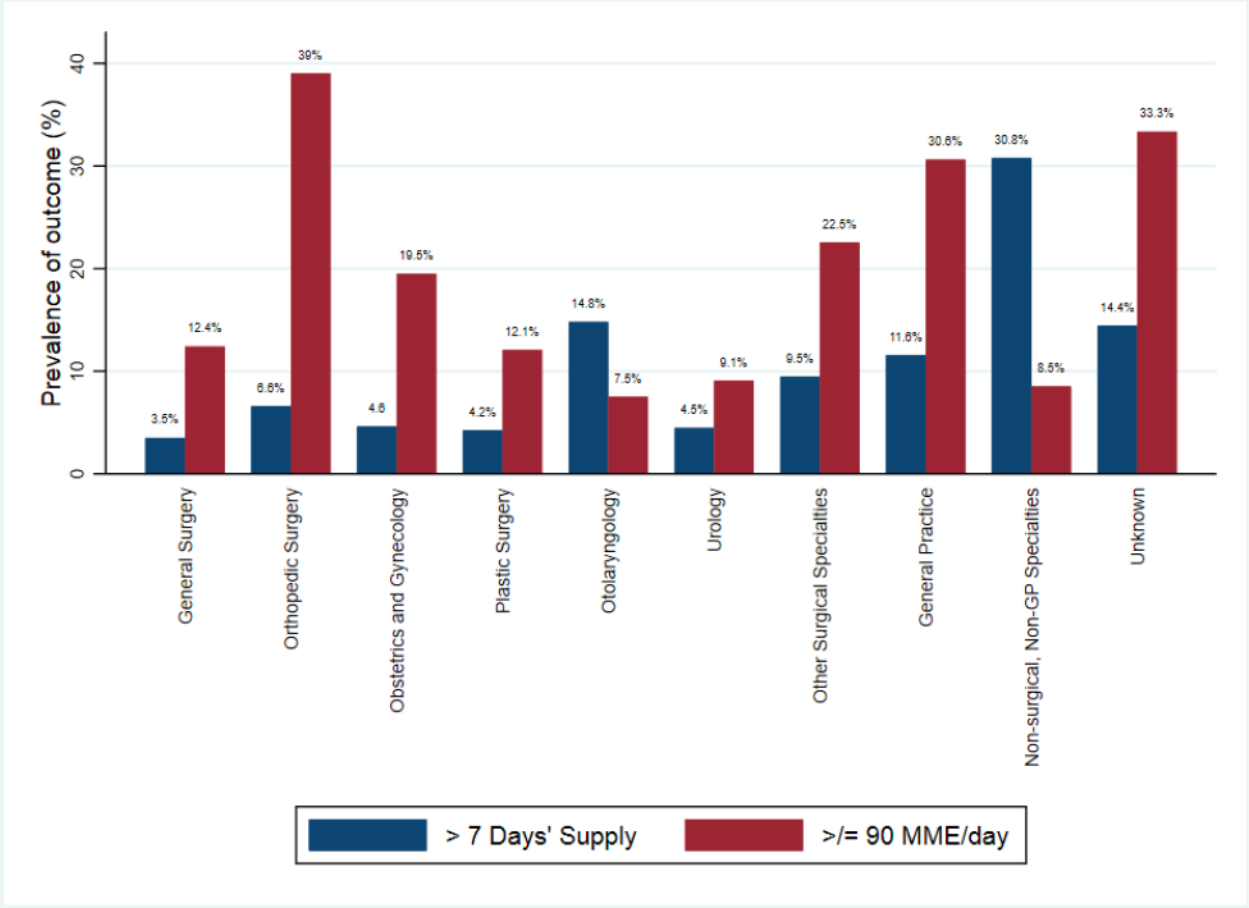


Table 4-1: Characteristics of the study population of opioid-naive adults who filled opioid prescriptions in community pharmacies within 14 days of surgical or emergency care in Nova Scotia, Canada (April 26th 2017 to March 31st 2019). (n= 36,716; column percentages presented)

		Overall (n= 36,716 unless otherwise indicated)		*Surgical care (n = 22,773)*		*Emergency care (n =10,271)*		*Emergency plus surgical care (n=3,672)*	
		n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Age and sex	*Age in years, mean (SD); range*	54.2 (17.5); 18-104		54.4 (16.7); 18 - 102		55.1 (18.7); 18 - 103		50.3 (18.2); 18 - 104	
	Female	20,147	54.8	12,871	56.5	5,436	52.9	1,840	50.1
Co-morbidities in past 12-months	*Hx of depression*	3,794	10.3	2,218	9.74	1,185	11.5	391	10.7
	Hx of anxiety	5,683	15.5	3,324	14.6	1,769	17.2	590	16.1
	Hx of alcohol abuse, or mental and behavioural disorders or physical illness due to alcohol use	620	1.70	338	1.48	179	1.74	103	2.81
	Hx of drug abuse, or mental and behavioural disorders due to drug use	317	0.86	161	0.71	104	1.01	52	1.42
	Hx of tobacco abuse, or mental and behavioural disorders due to tobacco use	3,051	8.31	1,915	8.41	591	5.75	545	14.8
	Hx of low back pain	6,461	17.6	2,967	13.0	3,039	29.6	455	12.4
	Hx of headache or migraine	838	2.29	499	2.19	267	2.60	72	1.96
	Hx of arthritis, joint pain or neck pain	20,735	56.5	13,703	60.2	4,929	48.0	2,103	57.3
	Hx of fibromyalgia	415	1.13	215	0.94	157	1.53	43	1.17
	Hx neuropathic pain	475	1.29	293	1.29	131	1.28	51	1.39
	Any cancer, except non-melanoma skin cancer	5,368	14.7	3,916	17.2	1,044	10.2	408	11.1
Type of procedure, if applicable (n= 26,445)	*Major Surgery*	20,543	77.7	18,472	81.1	-	-	2,071	56.4
	Minor Surgery	1,207	4.56	1,010	4.44	-	-	197	5.36
	Fracture, Dislocation, or Cast	1,809	6.84	805	3.53	-	-	1,004	27.3
	Bone Grafting	1,108	4.19	1,002	4.40	-	-	106	2.89
	Obstetrics	718	2.72	710	3.12	-	-	8	0.22
	Other	1,060	4.01	774	3.40	-	-	286	7.79
Procedure location, if applicable (n=26,445)	*Hospital*	24,230	91.6	21,001	92.2	-	-	3,229	87.9
	Office	1,155	4.40	998	4.38	-	-	157	4.28

	Unknown	1,060	4.00	774	3.40	-	-	786	7.79
Billing specialty of procedure provider, if applicable (n= 26,445)	*General Practice*	9,156	34.6	8,188	36.0	-	-	968	26.4
	Orthopedic Surgery	4,302	16.3	3,533	15.5	-	-	769	20.9
	General Surgery	4,041	15.3	3,181	14.0	-	-	860	23.4
	Obstetrics and Gynecology	2,709	10.2	2,566	11.3	-	-	143	3.89
	Plastic Surgery	1,508	5.70	1,269	5.57	-	-	239	6.51
	Otolaryngology	1,264	4.78	1,181	5.19	-	-	83	2.26
	Urology	1,208	4.57	1,041	4.57	-	-	167	4.55
	Other Surgical Specialties	898	3.40	788	3.46	-	-	110	3.00
	Other Non-surgical Specialties	299	1.13	252	1.11	-	-	47	1.28
	Unknown	1,060	4.01	774	3.40	-	-	286	7.79

ED emergency department; SD standard deviation; m months; Hx 12-month past history

Column percentages presented. Only 'yes' category presented for binary variables; all categories presented for variables with 3+ categories.

Undergoing procedures identified from MSI Physicians' Billings using Canadian Classification of Procedures (CCP) codes and CIHI DAD using the Canadian Classification of Health Interventions (CCI) codes after linkage to Drug Information System Database (DIS)

Emergency Department visits identified from NACRS database after linkage to DIS

Age in years on day of index opioid filling

12-month history of mental health illness, substance use, chronic pain, and cancer identified using International Classification Diseases 9th edition (ICD-9-CM) diagnostic codes and International Classification Diseases 10th edition Canadian enhanced version (ICD-10-CA) diagnostic codes in MSI Physicians' Billings and CIHI DAD databases, respectively. See Appendix 5 for full list of ICD codes.

Type of procedure identified using CCP codes in MSI Physicians' Billings Database; billing specialty of procedure provider identified from MSI Physicians' Billings Database

Table 4-2: Characteristics of first-prescription fills in community pharmacies in Nova Scotia (April 26th 2017 to March 31st 2019) by opioid-naive adults who filled opioid prescriptions within 14 days of surgical or emergency care in Nova Scotia, Canada, and prevalence of outcomes (n=36,716; column percentages presented)

				Overall (n=36,716)		*Surgical care (n = 22,773)*		*Emergency care (n =10,271)*		*Emergency plus surgical care (n=3,672)*	
				n	%	n	%	n	%	n	%
Characteristics		Type of opioid	*Codeine*	9,682	26.4	5,482	24.1	3,595	35.0	605	16.5
			Hydromorphone	18,370	50.0	12,706	55.8	3,215	31.3	2,449	66.7
			Oxycodone	2,579	7.02	1,799	7.90	562	5.47	218	5.94
			Morphine	2,876	7.83	1,130	4.96	1,503	14.6	243	6.62
			Tramadol	3,113	8.48	1,605	7.05	1,355	13.2	153	4.17
			Other	96	0.26	51	0.22	41	0.40	<5*	0.11
		Route	*Oral*	36,444	99.3	22,715	99.8	10,077	98.1	3,652	99.5
			Other	272	0.74	58	0.20	194	1.89	20	0.50
		Days' supply	*Median; range (IQR)*	3; 1 - 30	(2 – 5)	3; 1 - 30	(2 – 5)	4; 1 - 30	(2 – 5)	3; 1 - 30	(2 – 4)
			≤ 3 days	20,650	56.2	13,106	57.6	5,131	50.0	2,413	65.7
			4 – 7 days	12,082	32.9	7,678	33.7	3,401	33.1	1,003	27.3
			>7 days	3,984	10.9	1,989	8.73	1,739	16.9	256	6.97
		MME	*Total, median (IQR)*	150	(100 – 300)	150	(100 – 300)	135	(90 – 200)	150	(100 – 300)
			Daily, median (IQR)	50	(30 – 75)	50	(37.5 – 83.3)	36	(22.5 – 50)	50	(36 – 100)
		Multiple fills on index day	*Yes*	251	0.68	123	0.54	96	0.93	32	0.87
		ED visit to fill, if applicable	*Days, median (IQR)*	-	-	-	-	1	(0 – 2)	3	(1 – 6)
Outcomes	Main	>7 days' supply	*Yes*	3,984	10.9	1,989	8.73	1,739	16.9	256	6.97
		≥90 MME/day	*Yes*	7,369	20.2	5,506	24.2	909	9.02	954	26.1
		Long-acting	*Yes*	266	0.72	151	0.66	104	1.01	11	0.30

2ry	Strong opioid	*Yes*	23,921	65.2	15,686	68.9	5,321	51.8	2,914	79.4
	tramadol	*Yes*	3,113	8.48	1,605	7.05	1,355	13.2	153	4.17
Alternative	> 3 days' supply	*Yes*	16,066	43.8	9,667	42.5	5,140	50.0	1,259	34.3
	> 14 days' supply	*Yes*	1,257	3.42	454	1.99	722	7.03	81	2.21
	≥ 50 MME/day	*Yes*	18,930	51.9	13,511	59.5	3,141	31.2	2,278	62.4

*Cells with n <5 are indicated as such in the Table for privacy

ED emergency department; MME morphine milligram equivalents; IQR interquartile range; SD standard deviation

Strong opioids: Hydromorphone, oxycodone, morphine, fentanyl; Weak opioids: Codeine, tramadol.

MME total and per day are calculated for oral opioid formulations (n=36,444 ; 99.3% of cohort). This is the n included in all dose variables.

Table 4-3: Unadjusted and adjusted odds ratios (with 95% CI) for filling prescriptions >7 days' supply, ≥90MME/day, or for long-acting opioids based on setting and specialty of procedure provider among opioid-naive patients who had surgical or emergency care and filled opioid prescriptions between April 26th 2017 and March 31st 2019 in community pharmacies in Nova Scotia, Canada (setting n= 36,716; billing specialty n= 26,445; row percentages presented).

		>7 days' supply = yes (n setting=36,716; n specialty=26,445)			≥90 MME = yes (n setting=36,716; n specialty=26,445)			Long-acting opioid = yes (n setting=36,716; n specialty=26,445)		
		n (row %)	OR (95% CI)	aOR (95% CI)	n (row %)	OR (95% CI)	aOR (95% CI)	n* (row %)	OR (95% CI)	aOR (95% CI)
Setting (n= 36,716)	*Surgical care (n=22,773)*	**1,989 (8.73)**	Ref	Ref	**5,506 (24.2)**	Ref	Ref	**151 (0.66)**	Ref	Ref
	Emergency care (n=10,271)	**1,739 (16.9)**	2.13 (1.99– 2.28)	2.13 (1.98 – 2.29)	**909 (9.02)**	0.31 (0.29 – 0.33)	0.34 (0.31 – 0.37)	**104 (1.01)**	1.53 (1.19 – 1.97)	1.36 (1.04 – 1.77)
	Emergency plus surgical care (n=3,672)	**256 (6.97)**	0.78 (0.68 – 0.90)	0.86 (0.75 – 0.99)	**954 (26.1)**	1.11 (1.02 – 1.20)	1.07 (0.99– 1.16)	**< 5***	0.45 (0.24 – 0.83)	0.44 (0.23 – 0.82)
Billing specialty of procedure provider, for all subjects who had procedures (n= 26,445)	*General Surgery (n=4,041)*	**141 (3.51)**	Ref	Ref	**501 (12.4)**	Ref	Ref	**43 (1.06)**	Ref	Ref
	Orthopedic surgery (n=4,302)	**284 (6.60)**	1.94 (1.57 – 2.39)	1.17 (0.94 – 1.47)	**1,675 (39.0)**	4.52 (4.04 – 5.05)	2.92 (2.58 – 3.30)	**5 (0.12)**	0.11 (0.04 – 0.27)	0.17 (0.06 – 0.45)
	Obstetrics and Gynecology (n= 2,709)	**125 (4.61)**	1.33 (1.04 – 1.70)	1.46 (1.13 – 1.89)	**526 (19.5)**	1.71 (1.49 – 1.95)	1.94 (1.68 – 2.22)	**0 (0.00)**	-	-
	Plastic Surgery (n= 1,508)	**64 (4.24)**	1.22 (0.90 – 1.64)	1.03 (0.75 – 1.40)	**182 (12.1)**	0.97 (0.81 – 1.16)	0.74 (0.62 – 0.89)	**< 5***	0.12 (0.03 – 0.51)	0.16 (0.04 – 0.67)
	Otolaryngology (n=1,264)	**187 (14.8)**	4.77 (3.79 – 5.99)	4.89 (3.86 – 6.20)	**95 (7.52)**	0.57 (0.46 – 0.72)	0.63 (0.50 – 0.79)	**< 5***	0.07 (0.01 – 0.54)	0.07 (0.01 – 0.50)
	Urology (n= 1,208)	**54 (4.47)**	1.28 (0.93 – 1.77)	1.19 (0.86 – 1.65)	**109 (9.08)**	0.70 (0.57 – 0.88)	0.68 (0.54 – 0.85)	**13 (1.08)**	1.01 (0.54 – 1.89)	0.90 (0.48 – 1.70)
	Other Surgical Specialties (n=898)	**85 (9.47)**	2.87 (2.17 – 3.79)	2.52 (1.89 – 3.36)	**202 (22.5)**	2.05 (1.71 – 2.47)	1.52 (1.26 – 1.84)	**< 5***	0.10 (0.01 – 0.75)	0.09 (0.01 – 0.70)
	General practice (n=9,156)	**1,059 (11.6)**	3.59 (3.00 – 4.30)	2.31 (1.91 – 2.79)	**2,798 (30.6)**	3.11 (2.81 – 3.45)	2.45 (2.20 – 2.74)	**65 (0.71)**	0.66 (0.45 – 0.98)	0.89 (0.59 – 1.36)
	Non-surgical non general practice specialties (n=299)	**92 (30.8)**	12.2 (9.06 – 16.4)	6.66 (4.87 – 9.11)	**25 (8.53)**	0.66 (0.43 – 1.00)	0.74 (0.48 – 1.13)	**9 (3.01)**	2.89 (1.39 – 5.98)	2.12 (0.98 – 4.60)
	*Unknown** (n=1,060)*	**153 (14.4)**	4.63 (3.65 – 5.88)	5.35 (4.19 – 6.85)	**347 (33.3)**	3.53 (3.01 – 4.14)	3.06 (2.60 – 3.60)	**23 (2.17)**	2.06 (1.24 – 3.44)	2.10 (1.24 – 3.55)

* Cells with n <5 are indicated as such in the Table for privacy

** Billing specialty of procedure provider not available (CCI code)

Row percentages presented

MME Morphine Milligram Equivalent; OR odds ratio; aOR adjusted odds ratio; CI confidence interval

Undergoing procedures identified from MSI Physicians' Billings using Canadian Classification of Procedures (CCP) codes and CIHI DAD using the Canadian Classification of Health Interventions (CCI) codes after linkage to Drug Information System Database (DIS)

Emergency Department visits identified from NACRS database after linkage to DIS

Billing specialty of procedure provider identified from MSI Physicians' Billings Database

Other surgical specialties are cardiac surgery (n=135), neurosurgery (n=229), thoracic surgery (n=389), and vascular surgery (n=151)

Non-surgical non general practice specialties ranged from n=1 to n=144 in the following specialties: anaesthesia, cardiology, dermatology, diagnostic radiology, emergency medicine, gastroenterology, haematology, internal medicine, medical oncology, ophthalmology, optometry, pathology, psychiatry, radiation oncology, and respiratory medicine.

Covariates included in the adjusted models: patient age (continuous, in years) and sex (binary, female or male) on the day of opioid filling, binary variables (yes vs. no) measuring 12-month history of the following conditions: depression, anxiety, alcohol abuse, drug abuse, tobacco abuse, low back pain, headache, arthritis, fibromyalgia, neuropathic pain, and cancer (any cancer except non-melanoma skin cancer) – codes in Appendix 5. In the model for specialty of procedure provider, we also adjusted for procedure type (major surgery; minor surgery; fracture, dislocation, or cast; bone grafting; obstetrics; and other, which included procedures that were captured in DAD database but not MSI).

4.5 Appendices

Appendix 4-A: Results of secondary outcome analysis - Unadjusted and adjusted odds ratios (with 95% CI) for filling strong opioids and Tramadol based on setting and specialty of procedure provider among opioid naive patients who had surgical or emergency care and filled opioid prescriptions between April 26th 2017 and March 31st 2019 in community pharmacies in Nova Scotia, Canada (n= 36,716).

		Strong opioid (n setting=36,716; n specialty=26,445)			Tramadol (n setting=36,716; n specialty=26,445)		
		n (row %)	OR (95% CI)	aOR (95% CI)	n (row %)	OR (95% CI)	aOR (95% CI)
Setting	*Surgical care (n=22,773)*	**15,686 (68. 9)**	Ref	Ref	**1,605 (7.05)**	Ref	Ref
	Emergency care (n=10,271)	**5,321 (51.8)**	0.48 (0.46 – 0.51)	0.52 (0.50 – 0..55)	**1,355 (13.2)**	2.00 (1.86 – 2.16)	1.79 (1.66 – 1.94)
	Emergency plus surgical care (n=3,672)	**2,914 (79.4)**	1.74 (1.60 – 1.89)	1.76 (1.62 – 1.92)	**153 (4.17)**	0.57 (0.48 – 0.68)	0.57 (0.48 – 0.68)
Billing specialty of procedure provider, for all subjects who had procedures	*General Surgery (n=4,041)*	**2,615 (64.7)**	Ref	Ref	**520 (12.9)**	Ref	Ref
	Orthopedic surgery (n=4,302)	**3,203 (74.5)**	1.59 (1.45 – 1.75)	1.04 (0.94 – 1.16)	**48 (1.12)**	0.08 (0.06 – 0.10)	0.10 (0.08 – 0.14)
	Obstetrics and Gynecology (n= 2,709)	**2,282 (84.2)**	2.91 (2.58 – 3.29)	2.35 (2.06 – 2.67)	**41 (1.51)**	0.10 (0.08 – 0.14)	0.12 (0.09 – 0.17)
	Plastic Surgery (n= 1,508)	**618 (41.0)**	0.38 (0.33 – 0.43)	0.29 (0.25 – 0.33)	**274 (18.2)**	1.50 (1.28 – 1.76)	1.73 (1.46 – 2.04)
	Otolaryngology (n=1,264)	**481 (38.1)**	0.33 (0.29 – 0.38)	0.35 (0.30 – 0.40)	**311 (24.6)**	2.21 (1.89 – 2.59)	2.33 (1.98 – 2.73)
	Urology (n= 1,208)	**732 (60.6)**	0.84 (0.73 – 0.96)	0.79 (0.69 – 0.91)	**101 (8.36)**	0.59 (0.46 – 0.76)	0.64 (0.51 – 0.80)
	Other Surgical Specialties (n=898)	**653 (72.7)**	1.45 (1.24 – 1.71)	0.93 (0.79 – 1.10)	**72 (8.02)**	0.59 (0.46 – 0.76)	0.75 (0.57 – 0.98)
	General practice (n=9,156)	**6,971 (76.1)**	1.74 (1.60 – 1.88)	1.31 (1.20 – 1.43)	**318 (3.47)**	0.24 (0.21 – 0.28)	0.29 (0.24 – 0.33)
	Non-surgical non general practice specialties (n=299)	**128 (42.8)**	0.41 (0.32 – 0.52)	0.48 (0.37 – 0.61)	**37 (12.4)**	0.96 (0.67 – 1.37)	0.92 (0.64 – 1.32)
	Unknown (n=1,060)*	**917 (86.5)**	3.50 (2.90 – 4.22)	2.88 (2.38 – 3.49)	**36 (3.40)**	0.24 (0.17 – 0.34)	0.27 (0.19 – 0.38)

MME Morphine Milligram Equivalent; OR odds ratio; aOR adjusted odds ratio; CI confidence interval

* Billing specialty of procedure provider not available (CCI code)

Strong opioids: Hydromorphone, oxycodone, morphine, fentanyl; Weak opioids: Codeine, tramadol.

Undergoing procedures identified from MSI Physicians' Billings using Canadian Classification of Procedures (CCP) codes and CIHI DAD using the Canadian Classification of Health Interventions (CCI) codes after linkage to Drug Information System Database (DIS)

Emergency Department visits identified from NACRS database after linkage to DIS

Billing specialty of procedure provider identified from MSI Physicians' Billings Database

Covariates included in the adjusted models: patient age (continuous, in years) and sex (binary, female or male) on the day of opioid filling, binary variables (yes vs. no) measuring 12-month history of the following conditions: depression, anxiety, alcohol abuse, drug abuse, tobacco abuse, low back pain, headache, arthritis, fibromyalgia, neuropathic pain, and cancer (any cancer except non-melanoma skin cancer). In the model for specialty of procedure provider, we also adjusted for procedure type (major surgery; minor surgery; fracture, dislocation, or cast; bone grafting; obstetrics; and other, which included procedures that were captured in DAD database but not MSI).

Appendix 4-B: Summary of sensitivity analyses results for the association between setting of care, specialty of procedure provider and prescriptions > 7 days' supply. Adjusted odds ratios (with 95% CI) presented (n=36,716 unless otherwise indicated).

		Days' Supply >7 days (unless otherwise indicated: n setting=36,716; n specialty=26,445)					
		Adjusted OR (95% CI)					
		Main	**No history of cancer diagnosis in past 12-m (n= 31,348) [a]**	**ED visit only eligible if ≤ 2 days from fill (n= 32,191) [b]**	**Alternative definition provider specialty [c]**	**Outcome defined > 3 days [d]**	**Outcome defined > 14 days [d]**
Setting	*Surgical care*	**Ref**	Ref	Ref	-	Ref	Ref
	Emergency care	**2.13 (1.98 – 2.29)**	1.99 (1.84 – 2.16)	1.29 (1.18 – 1.41)	-	1.43 (1.36 – 1.50)	3.55 (3.13 – 4.02)
	Emergency plus surgical care	**0.86 (0.75 – 0.99)**	0.81 (0.70 – 0.94)	0.62 (0.48 – 0.79)	-	0.75 (0.70 – 0.81)	1.22 (0.96 – 1.55)
Billing specialty of procedure provider	*General Surgery*	**Ref**	Ref	-	Ref	Ref	Ref
	Orthopedic surgery	**1.17 (0.94 – 1.47)**	1.21 (0.94 – 1.55)	-	2.52 (2.11 – 3.01)	1.42 (1.28 – 1.57)	0.89 (0.57 – 1.38)
	Obstetrics and Gynecology	**1.46 (1.13 – 1.89)**	1.71 (1.29 – 2.26)	-	1.56 (1.23 – 1.97)	0.99 (0.88 – 1.11)	1.26 (0.78 – 2.04)
	Plastic Surgery	**1.03 (0.75 – 1.40)**	0.89 (0.62 – 1.28)	-	1.24 (0.92 – 1.66)	0.95 (0.83 – 1.09)	1.13 (0.64 – 1.99)
	Otolaryngology	**4.89 (3.86 – 6.20)**	5.36 (4.07 – 7.05)	-	5.62 (4.51 – 6.99)	3.38 (2.96 – 3.87)	2.68 (1.72 – 4.18)
	Urology	**1.19 (0.86 – 1.65)**	1.14 (0.75 – 1.74)	-	1.31 (0.96 – 1.79)	0.72 (0.62 – 0.84)	1.42 (0.83 – 2.42)
	Other Surgical Specialties	**2.52 (1.89 – 3.36)**	2.88 (2.02 – 4.09)	-	2.83 (2.16 – 3.72)		
	General practice	**2.31 (1.91 – 2.79)**	2.41 (1.93 – 3.00)	-	4.84 (3.86 – 6.05)	1.80 (1.65 – 1.96)	1.26 (0.87 – 1.81)
	Non-surgical non general practice specialties	**6.66 (4.87 – 9.11)**	7.33 (5.16 – 10.4)	-	8.03 (5.95 – 10.8)	2.96 (2.30 – 3.80)	
	Unknown	**5.35 (4.19 – 6.85)**	4.73 (3.50 – 6.40)	-	5.83 (4.64 – 7.33)	1.88 (1.63 – 2.17)	8.19 (5.49 – 12.2)

MME Morphine Milligram Equivalent; OR odds ratio; aOR adjusted odds ratio; CI confidence interval

* Billing specialty of procedure provider not available (CCI code)

Undergoing procedures identified from MSI Physicians' Billings using Canadian Classification of Procedures (CCP) codes and CIHI DAD using the Canadian Classification of Health Interventions (CCI) codes after linkage to Drug Information System Database (DIS)

Emergency Department visits identified from NACRS database after linkage to DIS

Billing specialty of procedure provider identified from MSI Physicians' Billings Database

Covariates included in the adjusted models: patient age (continuous, in years) and sex (binary, female or male) on the day of opioid filling, binary variables (yes vs. no) measuring 12-month history of the following conditions: depression, anxiety, alcohol abuse, drug abuse, tobacco abuse, low back pain, headache, arthritis, fibromyalgia, neuropathic pain, and cancer (any cancer except non-melanoma skin cancer) – codes in Appendix 5. In the model for specialty of procedure provider, we also adjusted for procedure type (major surgery; minor surgery; fracture, dislocation, or cast; bone grafting; obstetrics; and other, which included procedures that were captured in DAD database but not MSI).

[a] In this analysis, we excluded 5,368 subjects with a history of cancer in the past 12 months.

[b] Here we considered prescriptions to be related to an ED visit only if they were filled on or up to two days from the visit. This excluded 4,748 subjects.

[c] In this analysis, we recategorized 7,594 subjects whose procedures were billed by general practice to the second listed surgical specialty of their procedure provider (n= 2,159 moved to general surgery, n= 4,783 moved to orthopedic surgery, and n= 652 moved to obstetrics and gynecology)

[d] In this sensitivity analysis, we set the threshold for days' supply at 3 days and 14 days.

Appendix 4-C: Summary of results from sensitivity analyses for the association between setting of care, specialty of procedure provider and prescriptions ≥90MME/day. Adjusted odds ratios (with 95% CI) presented (n=36,716 unless otherwise indicated).

		Dose ≥ 90MME/day (unless otherwise indicated: n setting=36,716; n specialty=26,445)				
		Adjusted OR (95% CI)				
		Main	**No history of cancer diagnosis in past 12-m (n= 31,348) [a]**	**ED visit only eligible if ≤ 2 days from fill (n= 32,191) [b]**	**Alternative definition provider specialty [c]**	**Outcome defined as ≥50 MME/d [d]**
Setting	*Surgical care*	**Ref**	Ref	Ref	-	Ref
	Emergency care	**0.34 (0.31 – 0.37)**	0.33 (0.31 – 0.36)	0.38 (0.35 – 0.41)	-	0.34 (0.33 – 0.36)
	Emergency plus surgical care	**1.07 (0.99– 1.16)**	1.08 (1.00 – 1.18)	0.87 (0.76 – 0.99)	-	1.10 (1.03 – 1.19)
Billing specialty of procedure provider	*General Surgery*	**Ref**	Ref	-	Ref	Ref
	Orthopedic surgery	**2.92 (2.58 – 3.30)**	2.82 (2.46 – 3.23)	-	3.93 (3.54 – 4.34)	1.96 (1.77 – 2.17)
	Obstetrics and Gynecology	**1.94 (1.68 – 2.22)**	2.20 (1.88 – 2.57)	-	2.05 (1.81 – 2.31)	1.42 (1.28 – 1.58)
	Plastic Surgery	**0.74 (0.62 – 0.89)**	0.70 (0.57 – 0.86)	-	0.85 (0.71 – 1.01)	0.49 (0.44 – 0.56)
	Otolaryngology	**0.63 (0.50 – 0.79)**	0.62 (0.48 – 0.82)	-	0.61 (0.49 – 0.77)	0.76 (0.67 – 0.87)
	Urology	**0.68 (0.54 – 0.85)**	0.56 (0.41 – 0.76)	-	0.67 (0.54 – 0.82)	0.72 (0.63 – 0.83)
	Other Surgical Specialties	**1.52 (1.26 – 1.84)**	0.89 (0.68 – 1.17)	-	1.62 (1.35 – 1.93)	1.22 (1.05 – 1.42)
	General practice	**2.45 (2.20 – 2.74)**	2.46 (2.18 – 2.79)	-	1.41 (1.18 – 1.68)	1.69 (1.56 – 1.83)
	Non-surgical non general practice specialties	**0.74 (0.48 – 1.13)**	0.54 (0.31 – 0.93)	-	0.7 (0.50 – 1.17)	0.43 (0.33 – 0.57)
	Unknown	**3.06 (2.60 – 3.60)**	3.46 (2.87 – 4.17)	-	3.09 (2.65 – 3.59)	1.48 (1.29 – 1.71)

MME Morphine Milligram Equivalent; OR odds ratio; aOR adjusted odds ratio; CI confidence interval

* Billing specialty of procedure provider not available (CCI code)

Undergoing procedures identified from MSI Physicians' Billings using Canadian Classification of Procedures (CCP) codes and CIHI DAD using the Canadian Classification of Health Interventions (CCI) codes after linkage to Drug Information System Database (DIS)

Emergency Department visits identified from NACRS database after linkage to DIS

Billing specialty of procedure provider identified from MSI Physicians' Billings Database

Covariates included in the adjusted models: patient age (continuous, in years) and sex (binary, female or male) on the day of opioid filling, binary variables (yes vs. no) measuring 12-month history of the following conditions: depression, anxiety, alcohol abuse, drug

abuse, tobacco abuse, low back pain, headache, arthritis, fibromyalgia, neuropathic pain, and cancer (any cancer except non-melanoma skin cancer) – codes in Appendix 5. In the model for specialty of procedure provider, we also adjusted for procedure type (major surgery; minor surgery; fracture, dislocation, or cast; bone grafting; obstetrics; and other, which included procedures that were captured in DAD database but not MSI).

[a] In this analysis, we excluded 5,368 subjects with a history of cancer in the past 12 months.

[b] Here we considered prescriptions to be related to an ED visit only if they were filled on or up to two days from the visit. This excluded 4,748 subjects.

[c] In this analysis, we recategorized 7,594 subjects whose procedures were billed by general practice to the second listed surgical specialty of their procedure provider (n= 2,159 moved to general surgery, n= 4,783 moved to orthopedic surgery, and n= 652 moved to obstetrics and gynecology)

[d] In this sensitivity analysis, we set the threshold for dose at 50 MME/day.

Appendix 4-D: Summary of sensitivity analyses results for the association between setting of care, specialty of procedure provider and long-acting opioid prescriptions. Adjusted odds ratios (with 95% CI) presented (n=36,716 unless otherwise indicated).

		Long-acting (unless otherwise indicated: n setting=36,716; n specialty=26,445)			
		Adjusted OR (95% CI)			
		Main	**No history of cancer diagnosis in past 12-m (n= 31,348) [a]**	**ED visit only eligible if ≤ 2 days from fill (n= 32,191) [b]**	**Alternative definition provider specialty [c]**
Setting	*Surgical care*	**Ref**	Ref	Ref	-
	Emergency care	**1.36 (1.04 – 1.77)**	1.20 (0.89 – 1.62)	0.72 (0.51 - 1.02)	-
	Emergency plus surgical care	**0.44 (0.23 – 0.82)**	0.28 (0.12 – 0.63)	0.29 (0.09 – 0.93)	-
Billing specialty of procedure provider	*General Surgery*	**Ref**	Ref	-	Ref
	Orthopedic surgery	**0.17 (0.06 – 0.45)**	0.14 (0.05 – 0.42)	-	0.08 (0.04 – 0.15)
	Obstetrics and Gynecology	-	-	-	-
	Plastic Surgery	**0.16 (0.04 – 0.67)**	0.20 (0.05 – 0.84)	-	0.09 (0.02 – 0.35)
	Otolaryngology	**0.07 (0.01 – 0.50)**	-	-	0.05 (0.01 – 0.35)
	Urology	**0.90 (0.48 – 1.70)**	1.10 (0.54 – 2.23)	-	0.65 (0.36 – 1.17)
	Other Surgical Specialties	**0.09 (0.01 – 0.70)**	0.16 (0.02 – 1.20)	-	0.06 (0.01 – 0.43)
	General practice	**0.89 (0.59 – 1.36)**	0.84 (0.53 – 1.33)	-	0.28 (0.11 – 0.72)
	Non-surgical non general practice specialties	**2.12 (0.98 – 4.60)**	2.34 (1.02 – 5.29)	-	1.31 (0.62 – 2.76)
	Unknown	**2.10 (1.24 – 3.55)**	0.58 (0.23 – 1.51)	-	1.41 (0.87 – 2.27)

MME Morphine Milligram Equivalent; OR odds ratio; aOR adjusted odds ratio; CI confidence interval

* Billing specialty of procedure provider not available (CCI code)

Undergoing procedures identified from MSI Physicians' Billings using Canadian Classification of Procedures (CCP) codes and CIHI DAD using the Canadian Classification of Health Interventions (CCI) codes after linkage to Drug Information System Database (DIS)

Emergency Department visits identified from NACRS database after linkage to DIS

Billing specialty of procedure provider identified from MSI Physicians' Billings Database

Covariates included in the adjusted models: patient age (continuous, in years) and sex (binary, female or male) on the day of opioid filling, binary variables (yes vs. no) measuring 12-month history of the following conditions: depression, anxiety, alcohol abuse, drug abuse, tobacco abuse, low back pain, headache, arthritis, fibromyalgia, neuropathic pain, and cancer (any cancer except non-melanoma skin cancer) – codes in Appendix 5. In the model for specialty of procedure provider, we also adjusted for procedure type

(major surgery; minor surgery; fracture, dislocation, or cast; bone grafting; obstetrics; and other, which included procedures that were captured in DAD database but not MSI).

[a] In this analysis, we excluded 5,368 subjects with a history of cancer in the past 12 months.

[b] Here we considered prescriptions to be related to an ED visit only if they were filled on or up to two days from the visit. This excluded 4,748 subjects.

[c] In this analysis, we recategorized 7,594 subjects whose procedures were billed by general practice to the second listed surgical specialty of their procedure provider (n= 2,159 moved to general surgery, n= 4,783 moved to orthopedic surgery, and n= 652 moved to obstetrics and gynecology)

5 Chapter Five: Association between characteristics of first filled prescription and prolonged opioid use in opioid-naive patients after surgical and emergency care

5.1 Note to reader

I conducted this study in response to the results generated in Chapter 2 showing scarcity in existing evidence about the association between first-prescription factors, particularly long days' supply, high dose, and long-acting formulations, and prolonged opioid use, and its inconsistency across studies. Furthermore, evidence generated in Chapter 4 showed that long days' supply and high-dose prescribing patterns do exist for a proportion of opioid-naive patients receiving surgical and emergency care in Nova Scotia. Therefore, I wanted to investigate how these patterns of prescribing relate to risk of prolonged use after adjusting for important covariates, and to explore whether an interaction between dose and days' supply exists.

5.2 Manuscript information

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Student contribution to the manuscript: Roah Merdad conceived the research question and designed the study with support and advice from Drs. Jill Hayden and Mark Asbridge. Roah managed data, planned analyses, conducted and interpreted all analyses

with input from co-supervisors and other co-authors. She wrote the manuscript draft and revised all drafts.

5.3 Manuscript

5.3.1 Abstract

Importance: Few studies assessed the association between characteristics of first filled opioid prescription and prolonged opioid use in opioid-naive populations presenting to acute care settings. A weak overall association between higher average daily dose and prolonged use was found.

Objective: To assess whether the association between average daily dose and prolonged opioid use differs by days' supply of first filled prescription, adjusting for important co-variates.

Design: Population-based cohort study using six linked administrative databases.

Setting: Province of Nova Scotia, Canada, 2017 to 2019.

Participants: All opioid-naive adults who filled opioid prescriptions in community pharmacies in Nova Scotia within 14 days of surgical or emergency care.

Exposure(s): Average daily dose of first filled prescription measured as morphine milligram equivalents (MME)/day assessed at 3, 7, and 14 days' supply.

Main Outcome and Measure(s): Main outcome was prolonged opioid use defined as ≥1 opioid fill from 8-90 days after the index fill date and ≥1 additional fill from 91-180 days.

Results: Of 27,665 study subjects (mean age 53.4 years; 54.6% female), 3.5% (n=965) had prolonged use. A significant interaction between dose and days' supply was present

in multivariable regression analysis adjusting for patient characteristics, opioid type, and additional fills in the first week. Adjusted predicted probability (absolute risk) of prolonged use at the median dose of 50MME/day was 1.9% at 3 days' supply and 5.7% at 14 days' supply; for 90MME/day, risk increased from 2.1% at 3 days' supply to 9.2% at 14 days' supply, a >fourfold increase. At 14 days' supply, probability of prolonged opioid use increased incrementally as dose increased from 10MME/day to 150MME/day, while at 3 days' supply, no such difference was observed. Findings were consistent across clinical setting subgroups and outcome definitions.

Conclusions and Relevance: In opioid-naive subjects filling opioid prescriptions after surgical and emergency care, first prescriptions with greater days' supply and long-acting formulations were associated with greater risk of prolonged use. High-dose prescriptions were associated with greater risk of prolonged use only for prescriptions with longer duration. Other opioid-related harms like overdose and death must be considered in future studies for a more comprehensive understanding of risk.

5.3.2 Introduction

Prolonged opioid use is an important potential outcome following new opioid prescribing to opioid-naive populations in surgical and emergency care settings.[1-6] Unintended prolonged opioid use (i.e., beyond three months) is unfavorable in many patients, given the associated risks of overdose, developing opioid use disorder, and other harms.[7-11] Potential risk factors for prolonged opioid use include the dose, days' supply, and type of opioid prescribed. Few studies have assessed whether risk of prolonged use is greater when longer duration and higher dose prescriptions are given to opioid-naive populations following surgical and emergency care. Earlier studies in diverse opioid-naive pain populations reported inconsistent findings for an association between prescriptions with longer days' supply and prolonged use,[12-14] but recent studies found an increased, clinically important risk.[2,15,16] The association between average daily dose and prolonged use is weak in magnitude and less certain.[2,12-16]

Prescribing decisions are modifiable during a clinical encounter, creating an opportunity for harm reduction. Associations between prescribing factors and prolonged use can inform care for trauma patients or patients expected to experience severe pain in the first days postoperatively. These patients may require high-dose prescriptions to achieve pain relief and encourage early mobilization. Methodological limitations that contributed to the ambiguity of estimated associations in previous studies include inadequate adjustment for important confounders due to data availability,[2,16] using statistically-driven approaches to confounder selection,[12,14] and analysis of dose using crude categorization instead of continuous measures.[2,13-16] Furthermore, previous studies have not explored whether an interaction between dose and days' supply exists.

This study linked large, routinely collected databases to assess the association between first prescription characteristics measured on a continuous scale and prolonged opioid use. We considered a possible interaction between daily dose and days' supply while adjusting for a set of conceptually and clinically important covariates. The objectives of this study were to: (1) estimate the risk of prolonged opioid use following opioid filling after surgical and emergency care in opioid-naive adults in Nova Scotia, and (2) assess the association between average daily dose, days' supply, and type (long- versus short-acting) of first filled opioid prescription and prolonged use after adjusting for covariates, and (3) determine whether the association between dose and prolonged use differed by days' supply.

5.3.3 Methods

Study design and setting

This population-based cohort study used data from six routinely collected administrative databases in Nova Scotia, Canada. A schematic representation of study design is presented in supplementary material, Figure 3-2 (Chapter 3). Databases were linked using unique encoded identifiers at Health Data Nova Scotia, Dalhousie University, to create de-identified datasets accessible to the research team. This study was approved by the Health Sciences Research Ethics Board at Dalhousie University (REB# 2019-4896).

Data sources

We identified filled opioid prescriptions and obtained opioid prescription data from the provincial Drug Information System database; enrolment status, age and sex on day of filling from the Insured Patient Registry database; surgical procedures and

comorbidities from the MSI Physicians' Billings database and Canadian Institute for Health Information Discharge Abstract Database; emergency department visits from the National Ambulatory Care Reporting System; and death status during the follow-up period from the provincial Vital Statistics database (Table 3-1; Chapter 3).

Study population and selection criteria

We included all opioid-naive adults (≥18 years) who filled opioid prescriptions within 14 days of receiving surgical or emergency care. We identified all opioid prescriptions (Appendix 3-A; Chapter 3) filled in community pharmacies in Nova Scotia between April 26, 2017, and March 31, 2019. Then we excluded: (1) prescriptions filled by subjects who had another opioid fill in the previous 180 days; (2) formulations for cough or diarrhea relief; (3) prescriptions filled by subjects without continuous insurance enrolment in the 12-month look-back period; and (4) prescriptions filled by subjects who did not have at least one surgical code or emergency department code (Appendix 3-B; Chapter 3) during the 14-day look-back period.

We then excluded those with <180 days of follow-up data, death, or loss of health plan enrolment within 180 days of index date. We excluded 164 subjects post-hoc with prescriptions of >30 days' supply (likely not being treated for acute pain) or >200 morphine milligram equivalents (MME)/day (likely not naive). We excluded 96 subjects post-hoc who filled methadone or buprenorphine/naloxone formulations during follow-up in at least one of the first three post-index fills.

Study variables

Outcome: The main study outcome was prolonged opioid use, defined as ≥1 prescription opioid fill from 8-90 days after the index date and ≥1 additional fill from 91-180 days. For sensitivity analysis, we tested three other outcome definitions: ≥1 fill in 91-180 days from index date (less conservative definition); ≥4 fills with at least one in each of 8-90, 91-180, 181-270, and 271-365 days (more conservative definition); and ≥1 fill in 91-365 days, with at least 60 days' supply (POQI-4 definition).[17]

Prescription factors: The main exposures of interest were average daily dose of first filled prescription (continuous variable), days' supply of the prescription (continuous variable), and whether it was long- or short-acting (binary variable). We used the Ontario Drug Policy Research Network[18] guide to calculate the average daily dose in MME, multiplying strength by quantity and conversion factor, then dividing by number of days supplied. We considered all extended-release, long-acting, or sustained-release formulations as "long acting". To calculate MME/day for subjects with multiple opioid fills on index day, we summed dose across all filled prescriptions and divided by the days' supply for the longest prescription filled. We coded opioid type as long-acting when both long- and short-acting opioids were filled (details in Appendix 5-A).

Covariates: We selected analysis covariates based on patient characteristics previously associated with prolonged opioid use in opioid-naive populations after surgical and emergency care[19-23], clinical input, a conceptual framework about unintended prolonged opioid use[24], and a directed acyclic graph proposing the relationship between first-prescription factors and opioid-related harms.[25] We included age, sex, 12-month history of chronic pain, alcohol or drug abuse, tobacco use, depression or anxiety, and history of cancer, using ICD codes to measure comorbidities

(Appendix 3-D; Chapter 3). We also included a variable measuring additional opioid prescription fills in the first week, associated with prolonged use,[26] to assess risk independently of this factor.

Statistical analysis

We described study population and filled prescriptions characteristics using means with standard deviations and medians with interquartile ranges for continuous variables. We summarized categorical variables using frequencies and percentages. We reported risk as the proportion of study population meeting the main outcome definition. We used regression analysis to estimate crude and covariate-adjusted associations between days' supply (continuous), dose (continuous), type (long- versus short-acting), and the outcome. We presented the change in risk associated with one day increase in days' supply and 10MME/day increase in dose of the first filled prescription – more thresholds presented in Appendix 5-C. We considered an association to be of potential clinical importance if the odds ratio was ≥1.5 and its confidence interval did not cross the null value.

To assess interaction between dose and days' supply, we included an interaction term in the model, and estimated adjusted predicted probabilities of prolonged use (i.e., absolute risk) with 95% confidence intervals (CIs) for 20MME increments of dose values from 10MME/day to 150MME/day, setting days' supply at 3, 7, and 14 days,[27,28] while setting all other covariates at their mean values. Corresponding figures plotted the interaction and represent the predicted probabilities of prolonged use. We tested whether the slope at each selected days' supply value differed from zero (i.e., risk was not

constant over increasing dose at the days' supply value selected) and whether the slope for 7 and 14 days differed significantly from the slope for 3 days.

We conducted eight sensitivity analyses to check robustness of findings across subgroups (surgical care only, emergency care only, removing subjects with cancer in previous year, and removing subjects who had additional procedures during the follow-up period), alternative definitions of prolonged use, and an alternative analytic approach estimating the association between high-dose prescription (≥90MME/day) and prolonged use across three days' supply strata (≤3 days, 4-7 days, or >7 days) rather than testing for interaction. Stata-V15 was used for all data management and analyses.[29]

5.3.4 Results

Study population characteristics

A total of 27,665 subjects met study inclusion criteria (Figure 5-1). Mean age of subjects was 53.4 years (SD 17.2); 54.6% were female (Table 5-1). A 12-month history of depression, anxiety, alcohol abuse, and drug abuse each were present in 10.4%, 15.5%, 1.8%, and <1% of the study population, respectively. Low back pain diagnosis, arthritis or neck pain, and cancer were present in 17.8%, 56.6%, and 13.9%, respectively. Most subjects filled their opioid prescription following major surgery (51.1%), emergency care (27.4%), or surgical and emergency care (10.0%). Most filled prescriptions were for hydromorphone (49.8%) or codeine (27.4%), with <1% for long-acting opioids. Median days' supply was 3 days (IQR 2-5); median daily dose was 50MME/day (IQR 30-75). Prescriptions of >7 days' supply were filled by 10.4% of subjects; 20.7% of subjects filled prescriptions ≥90MME/day. Less than 1% filled multiple opioid prescriptions on

index day, and 6.6% filled one additional opioid prescription within the first week, while <1% filled ≥2 additional prescriptions.

Association between first prescription dose, days' supply, type, and prolonged opioid use

Prolonged opioid use was observed in 965 subjects (3.5%) using the main outcome definition, 3.6% using the POQI-4 definition, 7.4% using the less conservative definition, and 1.2% using the more conservative definition (Appendix 5-B). Adjusting for patient characteristics, additional fills in the first week, and prescription factors, each one-day increase in days' supply was associated with 11% increased odds of prolonged use (aOR 1.11, 95% CI 1.09, 1.13) (Table 5-2). When supply was increased ≥5 days, a potentially clinically important difference in risk was observed (5-day increase: aOR 1.67, 95% CI 1.53, 1.82; 10-day increase: aOR 2.78, 95% CI 2.34, 3.30) (Appendix 5-C). The association between higher average daily dose and prolonged use was weak (aOR 1.02, 95% CI 1.00, 1.02 for every 10MME/day increase). Interaction term between dose and days' supply was statistically significant (P<0.001) indicating the association between dose and prolonged use was not similar across all values of days' supply.

Predicted probability of prolonged use at 3, 7, and 14 days' supply across various dose levels

For the same daily dose, adjusted predicted probability of prolonged use differed across days' supply values (Table 5-3). At median 50MME/day, risk of prolonged use increased from 1.9% (95% CI 1.7, 2.1) at 3-days' supply to 2.8% (95% CI 2.6, 3.1) at 7-days' supply, and 5.7% (95% CI 4.7, 6.7) at 14-days' supply. At 90MME/day, the risk was 2.1% (95% CI 1.9, 2.3) at 3-days' supply, 3.6% (95% CI 3.1, 4.2) at 7-days' supply,

and 9.2% (95% CI 6.3, 12.2) at 14-days' supply. The difference was more pronounced as dose increased (Table 5-3).

Plots representing probability of prolonged use demonstrated when prescriptions were of longer duration, the slopes differed from zero, indicating the probability of prolonged opioid use increased as dose increased (Figure 5-2). This difference was not observed at 3 days' supply, indicating constant risk regardless of dose at this duration. The absolute difference in risk between 10MME/day and 150MME/day was <1% at 3 days' supply (P=0.039), 2.9% (P<0.001) at 7 days' supply, and 14.9% at 14 days (P<0.001). The difference between the slopes was statistically significant (7 versus 3 days, P<0.001; 14 versus 3 days P<0.001; 14 versus 7 days P=0.001) (Appendix 5-D).

Sensitivity analyses

Results were consistent when analyses were re-run for the surgical subgroup only, emergency subgroup only, the subgroup with no history of cancer in the previous year, and using the alternative outcome definitions and the alternative analysis approach (Appendix 5-E to 5-G; figures in Appendix 5-H). However, the association between long-acting opioids and prolonged use was not present in the surgical care subgroup and stronger in the emergency care subgroup – small n of long-acting opioid prescriptions in surgical group contributed to imprecision and must be considered. Results for the subgroup with no additional procedures or surgeries during follow-up were less precise. The observed differences between slopes for the day's supply values selected were less pronounced.

5.3.5 Discussion

We found that 3.5% of previously opioid-naive adults who filled opioid prescriptions in community pharmacies in Nova Scotia within 14 days of surgical or emergency care transitioned to prolonged opioid use. Longer duration prescriptions and long-acting formulations were associated with higher risk of prolonged use after adjusting for covariates. The association between dose and prolonged use differed by duration of filled prescription. These findings were consistent across various subgroups, outcome definitions, and analysis approaches.

Our finding that 3.5% of opioid-naive individuals transitioned to prolonged use is in the middle of previously reported risks of 0.88% to 6.2% in opioid-naive populations with acute pain in Canada.[2,15,16] Risk of prolonged opioid use was higher in populations for whom less was known about the intent for short- or long-term use, such as populations with low back[2] and musculoskeletal pain,[15] compared to populations with postoperative pain for whom intent for use is generally short-term. These clinical differences may explain the lower overall risk observed in our study, which was comprised mostly of surgical patients (73%). Gomes et al[15] reported a risk of 0.88% and measured opioid use up to one year from first prescription. We measured use to 180 days.

Our findings are consistent with studies that found first prescriptions of longer duration were associated with higher risk of prolonged use.[2,13,15,16] Our findings also concur with studies showing that first prescriptions for long-acting opioids are associated with prolonged use.[1,13,16] Some patients prescribed long-acting opioids may have intentionally been initiated for longer-term use, or may not have been opioid-naive at baseline. Non-naivety is a strong risk factor for prolonged use after opioid filling for

acute pain.[30,31] Our findings of a weak *overall* association between higher first prescription dose (>90MME/day) and prolonged use are consistent with three studies that found a weak association: aOR magnitudes of 1.15 for 90-200MME/day[15] and 1.2 for >90MME/day[16], and adjusted hazards ratio of 0.96 for probability of discontinuing use with ≥90MME/day[13]. Another study found a moderate association (aOR 1.6 for >90MME/day).[2] Two other studies found no significant association, but a weak effect size in the direction of higher risk of prolonged use with higher dose (aOR 1.02[14] and 1.03[12]). Their findings were limited due to either very low risk of outcome and subsequent uncertainty in findings,[14] or confounder selection using a statistically driven approach.[12,14]

Our finding that the association between opioid dose and prolonged use differs by the prescription duration adds new evidence to the literature. These Canadian results concur with US-based studies that reported higher *total perioperative* MME (i.e., a function of dose and supply combined) was associated with higher risk of prolonged use compared to lower doses in previously opioid-naive patients undergoing surgery.[1,4,5,23,32,33] Our findings highlight the need to look beyond main effects to understand the association between prescribing patterns and risk of prolonged use in opioid-naive populations.

Strengths and limitations

Strengths of this study include: a population-level cohort-design; objective outcome measures based on documented filled opioid prescriptions; utilization of population-level data sources and data linkage; examination of potential effect modification; and multiple sensitivity analyses to assess robustness of findings across

subgroups, outcome definitions, and alternative analysis approaches. These design and analysis elements are recommended when researching prescription opioid safety.[25]

This study has limitations. We do not know what proportion of those who filled prescriptions actually used them. Our definition of surgical and emergency care considered fills within two weeks of care to be related to those episodes. Some patients may have had other care episodes after which prescription opioids were filled within this period, which could have misclassified and included those who received opioids for chronic pain indications. Also, the potential misclassification of opioid naivety status when opioids were used illicitly or through diverted streams may have overestimated the risk of prolonged use. We do not expect this risk to differ between exposure groups, except in the long-acting opioid variable, which may have strengthened the observed association. The algorithms used to measure comorbidity relied on a minimum presence of one pertinent ICD code within 12 months of the index date. These algorithms are generally highly specific, but may not be sensitive; comorbid subjects were potentially misclassified to the non-diseased group. This misclassification would not have differed across values of dose and days' supply, limiting bias. Importantly, the measure of prolonged opioid use used in this study might not have sufficiently distinguished between continuous opioid use and recurrent interrupted short-term use during follow-up.[1] This may have overestimated prolonged use and misclassified some subjects as prolonged opioid users when they had separate short-term use events. We conducted multiple sensitivity analyses to explore the impact of our definition on study findings, including an analysis excluding subjects with additional procedures during follow up and analyses testing alternative, more conservative, outcome definitions. Still, alternative definitions

the require fills to span at least 90 days and to include 120 days' supply or 10 or more fills might be better measures of continuous use.[1]

Implications

This study expands our understanding of the safety of opioid prescribing patterns and informs the development of targeted interventions and clinical guidelines. Judicious opioid prescribing postoperatively and after emergency care are priorities in policy and research on preventing opioid-related harms.[34] Educational interventions can affect opioid prescriber behavior in the acute care setting.[35]

Currently, little guidance exists for opioid prescribing postoperatively and in the emergency care setting for opioid-naive individuals. Our findings suggest that 7-14 days' supply initial prescriptions may need to be avoided when possible in surgical and emergency settings where individuals receive prescriptions for acute pain. Our findings also suggest opportunities for safe, short-term use of high-dose opioids in the immediate postoperative or post-trauma post-discharge period. While this study adds valuable information to the evidence base, no single piece of evidence should independently direct care. Recommendations for practice change should rely on systematic review and assessment of certainty of all available evidence, and should consider all harms that are important to patients including developing opioid use disorder, overdose and death.

Conclusion

A small proportion of opioid-naive patients who filled opioid prescriptions after surgical and emergency care transitioned to prolonged use. First prescriptions with higher days' supply and long-acting formulations were associated with greater risk of prolonged

use. High-dose prescriptions were also associated with greater risk of prolonged use, when prescriptions were longer in duration. We recommend further research to replicate these findings across subgroups of opioid-naive populations to better support targeted guideline development. We also suggest that other opioid-related harms like overdose and death are considered in future studies for a more comprehensive understanding of risk.

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Figure 5-1: Study cohort creation

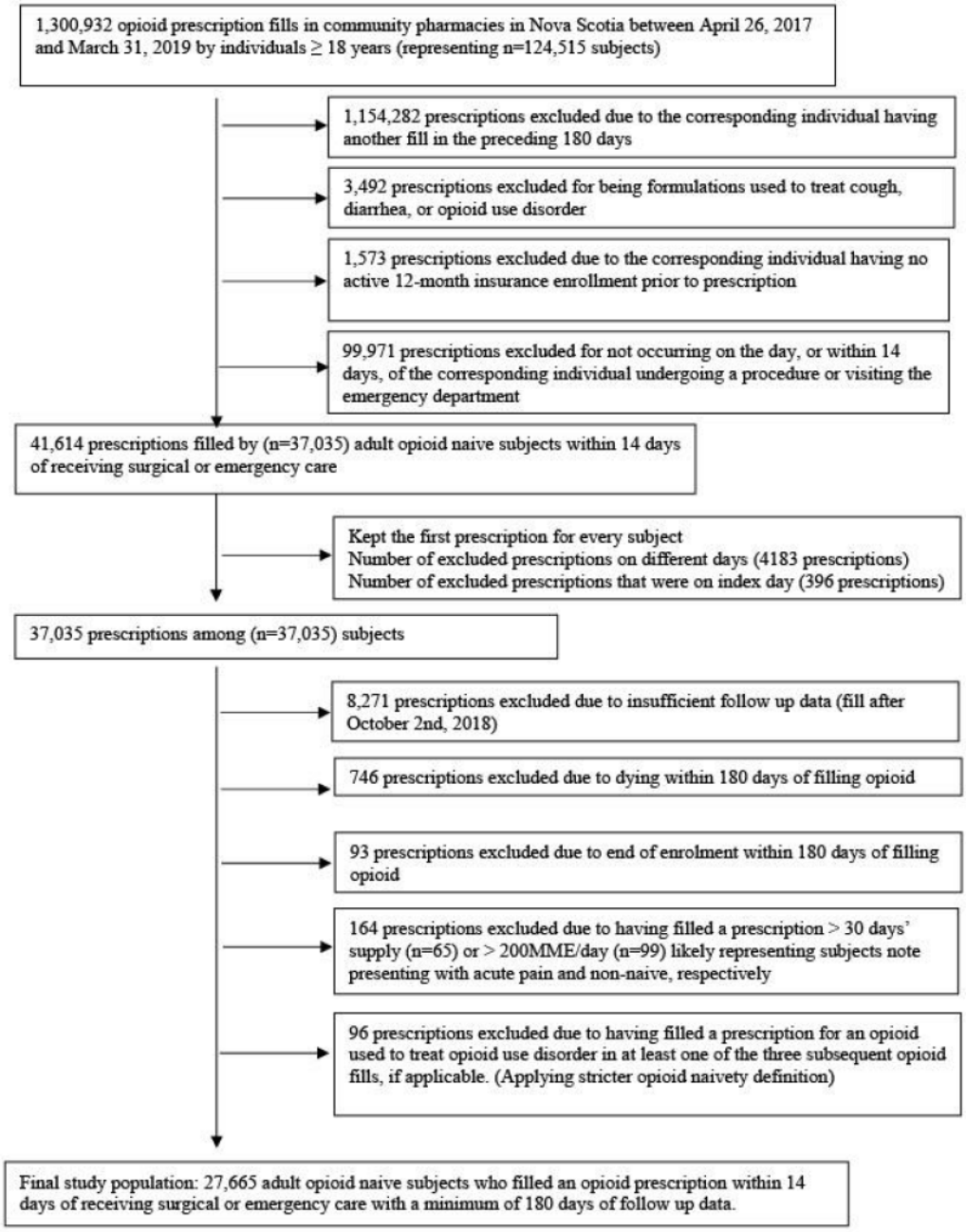


Figure 5-2: Predicted probabilities of prolonged opioid use for various dose values at 3, 7, and 14 days' supply (n= 27,665)

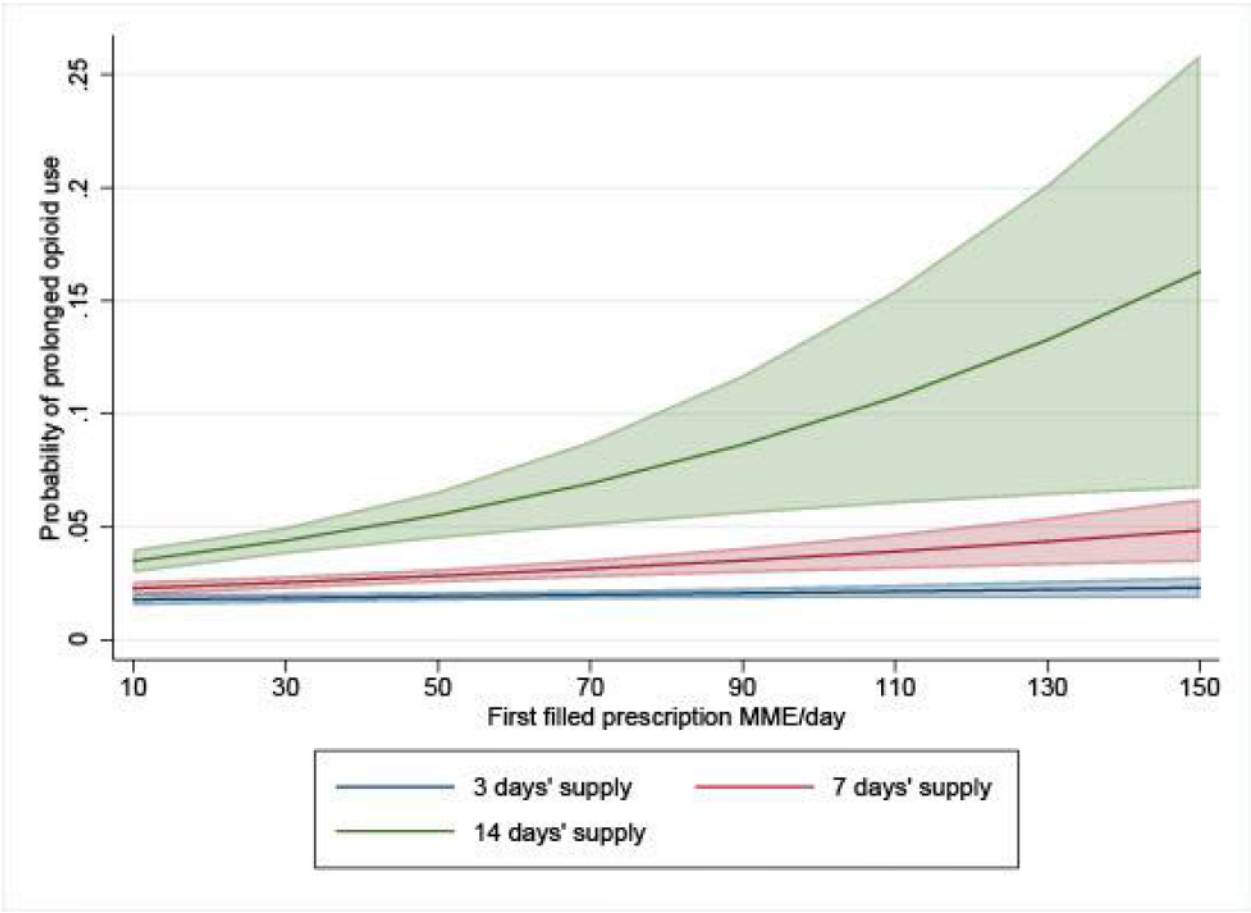

Probability of prolonged opioid use
0
.05
.1
.15
.2
.25
10
30
50
70
90
110
130
150
First filled prescription MME/day
3 days' supply
7 days' supply
14 days' supply

Table 5-1: Characteristics of study population (n= 27,665; column percentages presented)

		Overall (n= 27,665*)	
Factor	**Category [a]**	**n**	**%**
Age continuous, years [b]	*Mean (SD); range*	53.4 (17.2)	18-104
Age categorical, years	*18 to 35*	5,141	18.6
	36 to 45	3,817	13.8
	46 to 55	5,043	18.2
	56 to 65	6,144	22.2
	66 to 75	4,993	18.1
	>75	2,527	9.1
Sex	*Female*	15,117	54.6
Hx of depression [c]	*Yes*	2,874	10.4
Hx of anxiety [c]	*Yes*	4,285	15.5
Hx of alcohol abuse, or mental and behavioural disorders, or physical illness due to alcohol use [c]	*Yes*	485	1.8
Hx of drug abuse, or mental and behavioural disorders due to drug use [c]	*Yes*	249	0.90
Hx of tobacco abuse, or mental and behavioural disorders due to tobacco use [c]	*Yes*	2,716	9.8
Hx of low back pain [c]	*Yes*	4,913	17.8
Hx of headache [c]	*Yes*	662	2.4
Hx of arthritis, joint pain or neck pain [c]	*Yes*	15,669	56.6
Hx of fibromyalgia [c]	*Yes*	331	1.2
Hx neuropathic pain [c]	*Yes*	359	1.3
Any cancer, except non-melanoma skin cancer [c]	*Yes*	3,833	13.9
Care type [d]	*Major Surgery*	14,142	51.1
	Emergency care only	7,571	27.4
	Emergency care and surgical care	2,765	10.0
	Minor Surgery	805	2.9

	Bone Grafting	707	2.6
	Fracture, Dislocation, or Cast	595	2.2
	Obstetrics	562	2.0
	Unknown procedure	518	1.9
Type of opioid filled	*Codeine*	7,534	27.2
	Hydromorphone	13,778	49.8
	Oxycodone	2,007	7.3
	Morphine	2,017	7.3
	Tramadol	2,254	8.2
	Other	75	0.3
Long-acting opioid	*yes*	191	0.7
Strong opioid	*yes*	17,877	64.6
Route, oral	*yes*	27,589	99.7
Days' supply, total, continuous	*Median (IQR); range*	3 (2 – 5)	1 – 30
Days' supply, total, categorical	*≤3 days*	15,770	57.0
	4 – 7 days	9,009	32.6
	>7 days	2,886	10.4
MME, total of first filled prescription [e]	*Median (IQR); range*	150 (100 – 300)	5 – 3900
MME/day of first filled prescription [e]	*Median (IQR); range*	50 (30 – 75)	1 – 200
MME ≥ 90/day of first filled prescription [e]	*Yes*	5,727	20.8
Multiple fills on index day	*Yes*	161	0.6
Number of additional fills in first 7 days	*None*	25,687	92.9
	1	1,829	6.6
	≥ 2	149	0.5

SD standard deviation; IQR interquartile range; Hx 12-month medical history

[a] Only 'yes' category presented for binary variables; all categories presented for variables with 3+ categories.

[b] Age in years on day of index opioid filling

[c] 12-month history of mental health illness, substance use, chronic pain, and cancer identified using International Classification Diseases 9th edition (ICD-9-CM) diagnostic codes and International Classification Diseases 10th edition Canadian enhanced version (ICD-10-CA) diagnostic codes in MSI Physicians' Billings and CIHI DAD databases, respectively.

[d] Surgical care identified from MSI Physicians' Billings using Canadian Classification of Procedures (CCP) codes and CIHI DAD using the Canadian Classification of Health Interventions (CCI) codes after linkage to Drug Information System Database (DIS); Emergency care identified from emergency department visits identified from NACRS database after linkage to DIS; Type of procedure identified using CCP codes in MSI Physicians' Billings Database; we included the procedure most proximal to the index fill when there were multiple codes

[e] All dose variables calculated for subjects who filled opioids given through the oral route only (n=27,589). This is the denominator used in all categorical dose variables.

Table 5-2: Crude and adjusted odds ratios with 95% CI from logistic regression models estimating the association between first filled prescription factors and prolonged opioid use (n=27,665)

First filled prescription	Unit Change (supply, dose) [a] Category (type)	OR (95% CI) [n= 27,665]	aOR (95% CI) [c] [n= 27,665]
Supply, days, continuous [b]	1 day increase [d]	1.10 (1.09 – 1.11)	1.11 (1.09 – 1.13)
Dose, MME/day, continuous [b]	10 MME increase [d]	0.95 (0.93 – 0.96)	1.02 (1.00 – 1.04)
Type (long-acting)	Short acting	Ref	Ref
	Long acting	7.60 (5.33 – 10.8)	1.91 (1.20 – 3.02)

OR odds ratio; aOR adjusted odds ratio; CI confidence interval; MME Morphine Milligram Equivalent

[a] Days' supply and dose variables have been centred by subtracting the median values before entering in the model to reduce multicollinearity and improve interpretation.

[b] An interaction term was included in the multivariable model to test for interaction between dose and days' supply. The interaction terms were statistically significant (OR: 1.000816 (95% CI 1.000427 – 1.001206); aOR (1.001002 (1.000555 – 1.001449); p <0.001). A significant term means that the association between dose and prolonged use is not the same across all values of supply. It is not directly interpretable.

[c] The multivariable model was adjusted for age (continuous), sex (male, female), history of mental illnesses (yes if at least one of the following conditions was present: depression, anxiety), history of substance abuse (yes if at least one of the following conditions was present: alcohol abuse, drug abuse), history of tobacco abuse, history of chronic pain conditions (yes if at least one of the following conditions was present: low back pain, arthritis, neck pain, headache, fibromyalgia, or neuropathic pain), history of cancer (any cancer except non-melanoma skin cancer), and additional fills in the first seven days (none, one, ≥ 2), and all other prescription factors presented.

[d] See Appendix 5-C for additional days' supply and dose values.

Table 5-3: Adjusted predicted probabilities* of prolonged opioid use (with 95% CI) for various prescription doses at 3, 7, and 14 days' supply

	3 days' supply		7 days' supply		14 days' supply	
Dose, MME/day	**Point estimate (%)**	**95% CI**	**Point estimate (%)**	**95% CI**	**Point estimate (%)**	**95% CI**
10	1.75	1.50 – 2.00	2.24	1.94 – 2.53	3.41	2.91 – 3.92
30	1.83	1.61 – 2.04	2.52	2.25 – 2.79	4.40	3.82 – 4.99
50	1.91	1.72 – 2.10	2.84	2.55 – 3.14	5.65	4.65 – 6.65
70	1.99	1.80 – 2.18	3.21	2.83 – 3.56	7.23	5.44 – 9.02
90	2.08	1.85 – 2.31	3.61	3.08 – 4.15	9.22	6.25 – 12.2
110	2.17	1.87 – 2.46	4.07	3.32 – 4.82	11.7	7.05 – 16.3
130	2.26	1.89– 2.63	4.58	3.55 – 5.60	14.7	7.87 – 21.5
150	2.36	1.89 – 2.83	5.15	3.78 – 6.51	18.3	8.72 – 27.8

*Values correspond to plot in Figure 5-2, and represent an expansion of the interaction between average daily dose and days' supply that was identified in the multivariable model presented in Table 5-2.

5.5 Appendices

Appendix 5-A. Additional information about study variables

MME calculation formula, oral opioid analgesic conversion factors. *(Source: Ontario Drug Policy Research Network. ODPRN suggested calculation of opioid milligrams of morphine equivalents. Toronto: Ontario Drug Policy Research Network; November 2020.)*

Opioid		Ratio (Opioid : Morphine)
Morphine	30 mg	1:1
Codeine	200 mg	1:0.15
Oxycodone	15-20 mg	1:1.5
Hydrocodone	30 mg	1:1
Hydromorphone	6-7.5 mg	1:5
Meperidine	300 mg	1:0.1
Tramadol	300 mg	1:0.1

We used the following formula to calculate dose: MME=quantity * strength * conversion factor. We used the conversion factors as described in the Table, and divided the total MME by days' supply to estimate the average daily MME. Only opioids taken through the oral route were included in dose calculations. We decided post-hoc to truncate days' supply at 30 days and dose at 200 MME/day. The number of excluded subjects who exceeded these thresholds were 65 and 99 for days' supply and dose, respectively. These decisions had no impact on study outcomes.

Definition of short and long-acting opioids: All formulations that were labeled as extended-release, sustained-release, or long-acting were considered long-acting opioids, while all other formulations were considered short-acting.

Co-variates

We included age (continuous, in years) and sex (binary, male vs. female) which we obtained from the MASTER database, and history of the following conditions which were recorded as yes if a subject had a minimum of one diagnostic code assigned during a recorded healthcare visit over the previous 12 months: history of mental illnesses (yes with at least one code for depression or anxiety present), history of substance abuse (yes with at least one code for alcohol abuse or drug abuse present), history of tobacco abuse if at least one related code was present, history of chronic pain (yes with at least one code for any of the following conditions present: low back pain, arthritis, neck pain, headache, fibromyalgia, or neuropathic pain), history of cancer (yes if codes for any cancer diagnosis was present except non-melanoma skin cancer). We defined each comorbidity using a group of ICD-9-CM and ICD-10-CA codes presented in Appendix 3-D. We also included a co-variate measuring number of additional opioid prescriptions filled in the first week (categorized into none, one additional fill, or two or more) and for each of the risk factors assessed, we considered other prescription factors as co-variates of relevance.

Appendix 5-B: Risk of prolonged opioid use in main and alternative cohorts using main and alternative outcome definitions (n=27,665 unless otherwise indicated; column percentages presented).

		Main cohort		**Alternative cohorts (Sensitivity analysis)**			
		(n= 27,665; n=18,525 for persistent opioid use and more conservative outcome)		Excluding subjects with a history of cancer in the past 12 months (n= 23,832; n=15,964 for persistent opioid use and more conservative outcome)		Excluding subjects with one or more procedures in 180 days of follow up (n= 18, 314; n=11,516 for persistent opioid use and more conservative outcome)	
	Definition	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Main outcome (prolonged opioid use)	*≥ 2 fills, with at least one in each of 8 to 90 days and 91 to 180 days from index fill*	965/27,665	**3.5**	720/23,832	*3.0*	448/18,314	*2.5*
Alternative outcome definitions (sensitivity analysis)	*≥ 1 fill in 91 to 365 days from index fill with at least 60 days' supply* **(POQI-4 definition)***	661/18,525	**3.6**	513/15,964	*3.2*	313/11,516	*2.7*
	≥ 1 fill in 91 to 180 days from index fill **(less conservative definition)**	2,048/27,665	**7.4**	1,599/23,832	*6.7*	853/18,314	*4.7*
	≥ 4 fills with at least one in each of 8 to 90; 91 to 180; 181 to 270; 271 to 365 days from index fill **(more conservative definition)***	216/18,525	**1.2**	167/15,964	*1.1*	107/11,516	*0.9*

*POQI-4 definition and the more conservative outcome definition of prolonged use were calculated for subjects with 365+ days of follow up data (by excluding those with death between 181 and 365 days (n=416), and those with no sufficient follow up period (n=8,724)

Appendix 5-C: Results from logistic regression models estimating the association between days' supply, average daily dose, and type of first filled prescription and prolonged opioid use. (n=27,665; row percentage presented for the outcome)

First filled prescription	Unit Change (supply, dose) Category (type)	OR (95% CI) [n= 27,665]	aOR (95% CI) [n= 27,665]
Supply, days, continuous*	1 day increase	1.10 (1.09 – 1.11)	1.11 (1.09 – 1.13)
	3 day increase	1.33 (1.29 – 1.36)	1.36 (1.29 – 1.43)
	5 day increase	1.60 (1.53 – 1.67)	1.67 (1.53 – 1.82)
	7 day increase	1.93 (1.82 – 2.05)	2.05 (1.81 – 2.31)
	10 day increase	2.56 (2.35 – 2.80)	2.78 (2.34 – 3.30)
Dose, MME/day, continuous*	1 MME increase	0.99 (0.99 – 1.00)	1.00 (1.00 – 1.00)
	5 MME increase	0.97 (0.96 – 0.98)	1.01 (1.00 - 1.02)
	10 MME increase	0.95 (0.93 – 0.96)	1.02 (1.00 – 1.04)
	20 MME increase	0.89 (0.86 – 0.93)	1.04 (1.00 – 1.09)
	40 MME increase	0.80 (0.74 – 0.86)	1.09 (1.00 – 1.18)
Type (long-acting)	Short acting	Ref	Ref
	Long acting	7.60 (5.33 – 10.8)	1.91 (1.20 – 3.02)

OR odds ratio; aOR adjusted odds ratio; CI confidence interval; MME Morphine Milligram Equivalent

Days' supply and dose variables have been centred by subtracting the median values to reduce multicollinearity and improve interpretation.

*An interaction term was included in the multivariable model to test for interaction between dose and days' supply. The interaction terms were statistically significant in ($p < 0.001$). A significant term means that the association between dose and prolonged use is not the same across all values of supply.

The multivariable model was adjusted for age (continuous), sex (male, female), history of mental illnesses (yes if at least one of the following conditions was present: depression, anxiety), history of substance abuse (yes if at least one of the following conditions was present: alcohol abuse, drug abuse), history of tobacco abuse, history of chronic pain conditions (yes if at least one of the following conditions was present: low back pain, arthritis, neck pain, headache, fibromyalgia, or neuropathic pain), history of cancer (any cancer except non-melanoma skin cancer), multiple prescription opioid fills on index day (yes vs. no), and additional fills in the first seven days (none, one, ≥ 2), and all other prescription factors presented.

Appendix 5-D: Days' supply strata slopes.

Difference from zero	dy/dx	95% CI		P-value
3 days	0.00006	2.85 e-06	0.0001	0.039
7 days	0.00024	0.0001	0.0004	<0.001
14 days	0.00097	0.0005	0.0015	<0.001
Contrast between slopes	**contrast dy/dx**	**95% CI**		**P-value**
7 vs. 3 days	0.0002	0.0001	0.0003	<0.001
14 vs. 3 days	0.0009	0.0004	0.0014	<0.001
14 vs. 7 days	0.0007	0.0003	0.0011	0.001

Appendix 5-E: Sensitivity analysis: Results from logistic regression models estimating the association between days' supply, average daily dose, and type of first filled prescription and prolonged opioid use in alternative cohorts and using alternative outcome definitions

			Alternative cohorts				Alternative outcome definition		
		Main analysis	Surgical care cohort only	Emergency care cohort only	No history of cancer in past year	No procedure during follow up	Less conservative ≥ 1 fill in 91 – 180 days of follow up	More conservative ≥ 4 fills in each quarter of follow up	POQI-4 ≥ 1 fill in 91 to 365 days from index fill with at least 60 days' supply –
First filled prescription	**Unit Change (supply, dose) Category (type)**	**aOR (95% CI) [n= 27,665]**	**aOR (95% CI) [n= 20,094]**	**aOR (95% CI) [n= 10,336]**	**aOR (95% CI) [n= 23,832]**	**aOR (95% CI) [n=18, 314]**	**aOR (95% CI) [n=27,665]**	**aOR (95% CI) [n=18,52 5]**	**aOR (95% CI) [n=18,52 5]**
Supply, days, continuous*	*1 day increase*	1.11 (1.09 – 1.13)	1.12 (1.10 – 1.15)	1.10 (1.08 – 1.13)	1.10 (1.08 – 1.12)	1.09 (1.06 – 1.12)	1.07 (1.06 – 1.09)	1.10 (1.07 – 1.13)	1.12 (1.10 – 1.15)
	3 day increase	1.36 (1.29 – 1.43)	1.42 (1.32 – 1.52)	1.34 (1.25 – 1.44)	1.33 (1.26 – 1.42)	1.30 (1.20 – 1.41)	1.23 (1.86 – 1.29)	1.33 (1.23 – 1.45)	1.41 (1.33 – 1.51)
	5 day increase	1.67 (1.53 – 1.82)	1.79 (1.59 – 2.02)	1.63 (1.45 – 1.84)	1.62 (1.46 – 1.79)	1.55 (1.36 – 1.77)	1.42 (1.33 – 1.52)	1.62 (1.41 – 1.86)	1.78 (1.60 – 1.98)
	7 day increase	2.05 (1.81 – 2.31)	2.26 (1.92 – 2.67)	1.99 (1.69 – 2.34)	1.96 (1.70 – 2.25)	1.85 (1.54 – 2.22)	1.64 (1.49 – 1.80)	1.96 (1.62 – 2.38)	2.24 (1.93 – 2.60)
	10 day increase	2.78 (2.34 – 3.30)	3.21 (2.54 – 4.07)	2.67 (2.11 – 3.38)	2.61 (2.14 – 3.19)	2.41 (1.86 – 3.13)	2.02 (1.76 – 2.31)	2.62 (1.99 – 3.45)	3.17 (2.56 – 3.91)
Dose, MME/day, continuous*	*1 MME increase*	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)
	5 MME increase	1.01 (1.00 - 1.02)	1.02 (1.01 – 1.03)	1.00 (0.98 – 1.01)	1.00 (1.00 – 1.02)	1.01 (1.00 – 1.03)	1.00 (0.99 – 1.01)	1.00 (0.98 – 1.03)	1.00 (0.98 – 1.01)
	10 MME increase	1.02 (1.00 – 1.04)	1.04 (1.01 – 1.07)	0.99 (0.96 – 1.03)	1.01 (0.99 – 1.04)	1.01 (0.99 – 1.06)	1.00 (0.99 – 1.01)	1.00 (0.96 – 1.05)	1.00 (0.97 – 1.02)
	20 MME increase	1.04 (1.00 – 1.09)	1.08 (1.03 – 1.14)	0.99 (0.93 – 1.06)	1.03 (0.98 – 1.08)	1.05 (0.98 – 1.11)	1.00 (0.97 – 1.03)	1.01 (0.91 – 1.11)	0.99 (0.94 – 1.05)
	40 MME increase	1.09 (1.00 – 1.18)	1.16 (1.05 – 1.29)	0.98 (0.87 – 1.11)	1.06 (0.96 – 1.17)	1.10 (0.97 – 1.24)	1.01 (0.95 – 1.06)	1.01 (0.84 – 1.22)	0.99 (0.89 – 1.10)
Type	*Short acting*	Ref	Ref		Ref	Ref	Ref	Ref	Ref
	Long acting	1.91 (1.20 – 3.02)	0.84 (0.34 – 2.03)	2.87 (1.67 – 4.94)	2.11 (1.26 – 3.55)	2.58 (1.36 – 4.88)	2.31 (1.60 – 3.34)	2.57 (1.24 – 5.31)	1.81 (1.03 – 3.17)

No history of cancer - Excluding 3,833 subjects with a history of cancer in past 12 months; No procedure during follow up – Excluding 9,351 subjects with one or more procedures in 180 days of follow up; More conservative and POQI-4 outcome definition excluding those with death between 181 and 365 days (n=416), and those with no sufficient follow up period (n=8,724)

Appendix 5-F: Sensitivity analysis: Logistic regression estimating the association between high daily dose of first filled prescription (≥ 90 MME/day) and prolonged opioid stratified by days' supply (n=27,665; row percentage presented for the outcome)

					Stratified by days' supply of prescription											
	Overall (n=27,665)				≤ 3 days' supply (n= 15,770)				4 – 7 days' supply (n= 9,009)				> 7 days' supply (n= 2,886)			
Category	Total n in row	Outcome n (%)	OR (95 % CI)	aOR (95 % CI)	Total n in row	Outcome n (%)	OR (95 % CI)	aOR (95 % CI)	Total n in row	Outcome n (%)	OR (95 % CI)	aOR (95 % CI)	Total n in row	Outcome n (%)	OR (95 % CI)	aOR (95% CI)
< 90 MME/d	21,894	795	Ref	Ref	12,039	274 (2.28)	Ref	Ref	7,116	286 (4.02)	Ref	Ref	2,754	235 (8.55)	Ref	Ref
≥ 90 MME/d	5,771	170	0.81 (0.68 – 0.95)	1.02 (0.84 – 1.22)	3,784	88 (2.33)	1.02 (0.80 – 1.30)	1.00 (0.77 – 1.30)	1,875	68 (3.61)	0.89 (0.68 – 1.17)	1.50 (1.11 – 2.04)	97	14 (13.6)	1.68 (0.94 – 3.00)	2.80 (1.43 – 5.49)

OR odds ratio; aOR adjusted odds ratio; CI confidence interval; MME Morphine Milligram Equivalent

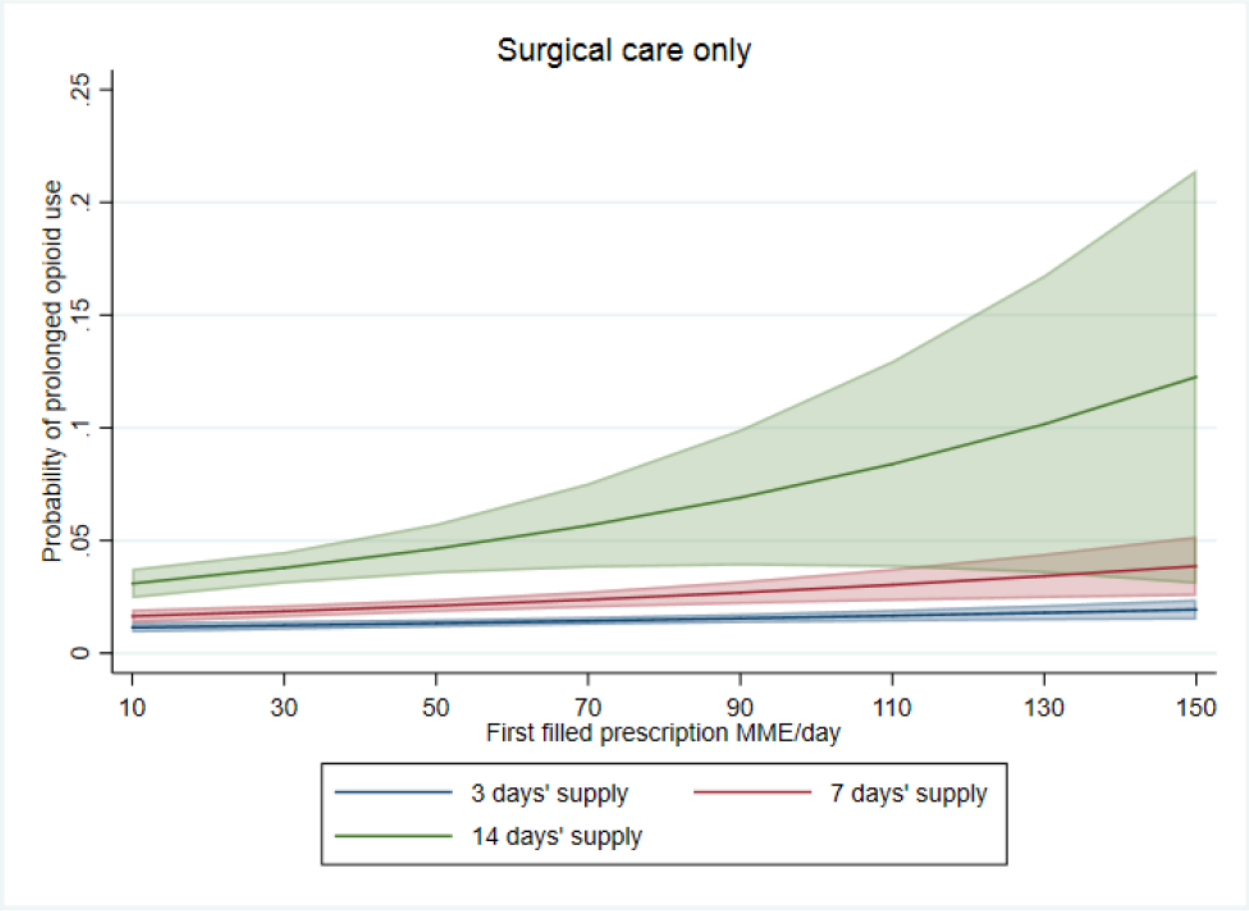
Multivariable models adjusted for age (continuous), sex (male, female), history of mental illnesses (yes if at least one of the following conditions was present: depression, anxiety), history of substance abuse (yes if at least one of the following conditions was present: alcohol abuse, drug abuse), history of tobacco abuse, history of chronic pain conditions (yes if at least one of the following conditions was present: low back pain, arthritis, neck pain, headache, fibromyalgia, neuropathic pain), history of cancer (any cancer except non-melanoma skin cancer), type of opioid (short- vs. long-acting) whether multiple opioid prescriptions were filled in index day (no vs. yes), and number of additional opioid prescriptions in the first week (none, one, or two or more).

Appendix 5-G: Sensitivity analysis: Days' supply strata slopes across sensitivity analysis groups.

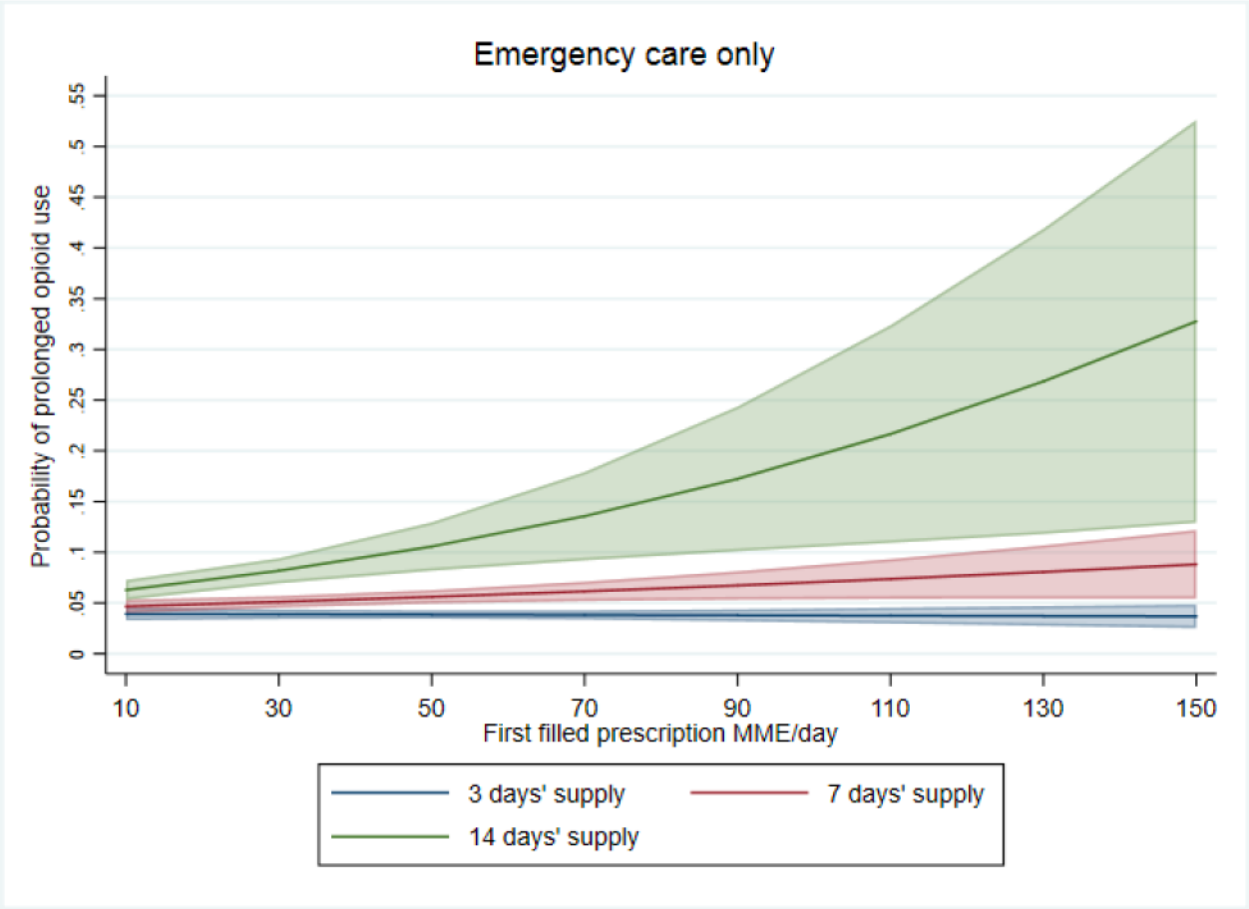
	Main	Surgical care cohort only	Emergency care cohort only	No history of cancer in past year	No procedure during follow up	Less conservative outcome definition	More conservative outcome definition	POQI-4 outcomr definition
Difference from zero	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**
3 days	0.039	0.004	0.777	0.239	0.144	0.848	0.907	0.788
7 days	<0.001	0.001	0.012	0.001	0.031	0.027	0.525	0.064
14 days	<0.001	0.029	0.002	0.004	0.087	0.013	0.380	0.022
Contrast between slopes	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**	**P-value**
7 vs. 3 days	<0.001	0.014	<0.001	0.001	0.072	0.007	0.338	0.008
14 vs. 3 days	<0.001	0.048	0.001	0.005	0.123	0.013	0.369	0.019
14 vs. 7 days	0.001	0.059	0.002	0.008	0.139	0.016	0.378	0.022

Appendix 5-H: Figures of sensitivity analyses results

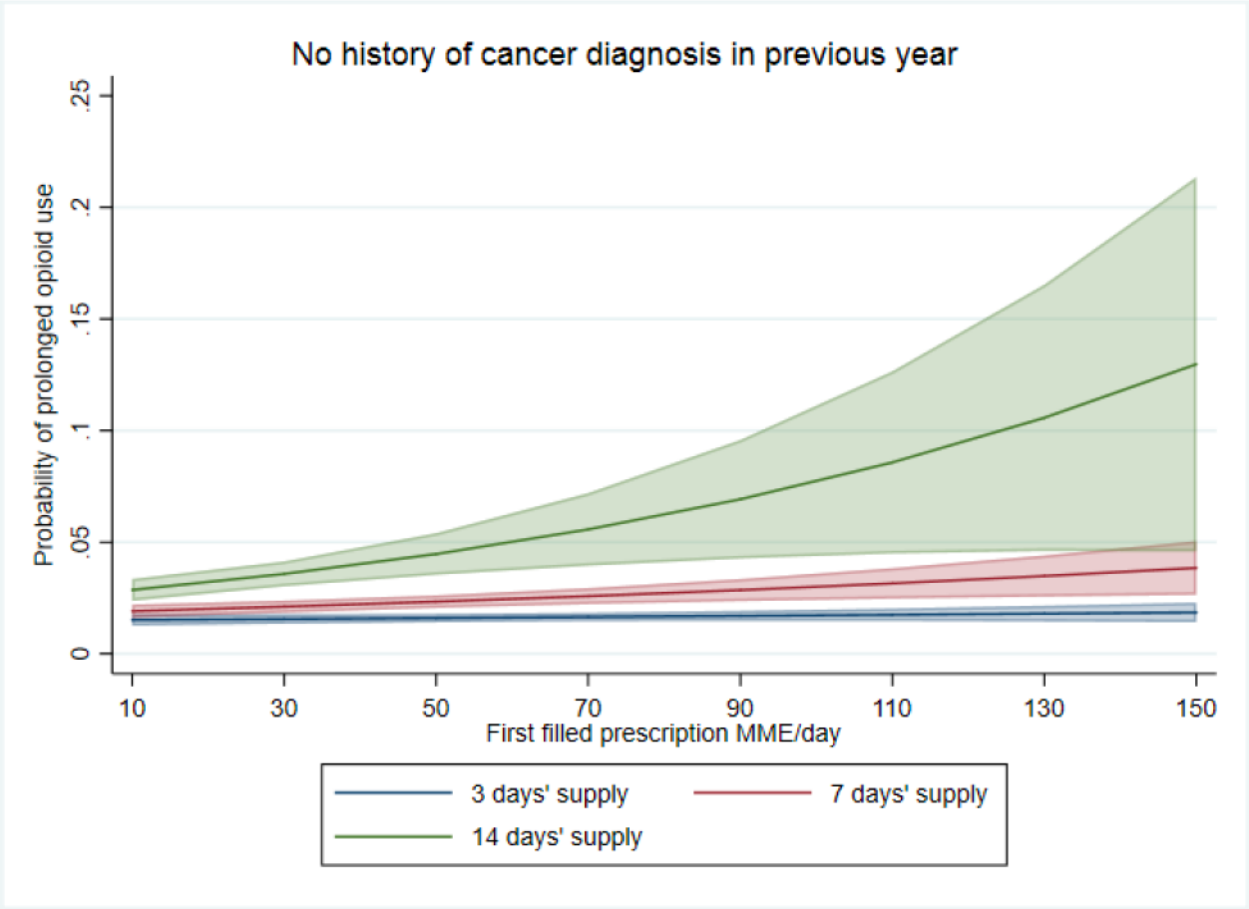
5-H-1: Surgical care subgroup only (n= 20,094)



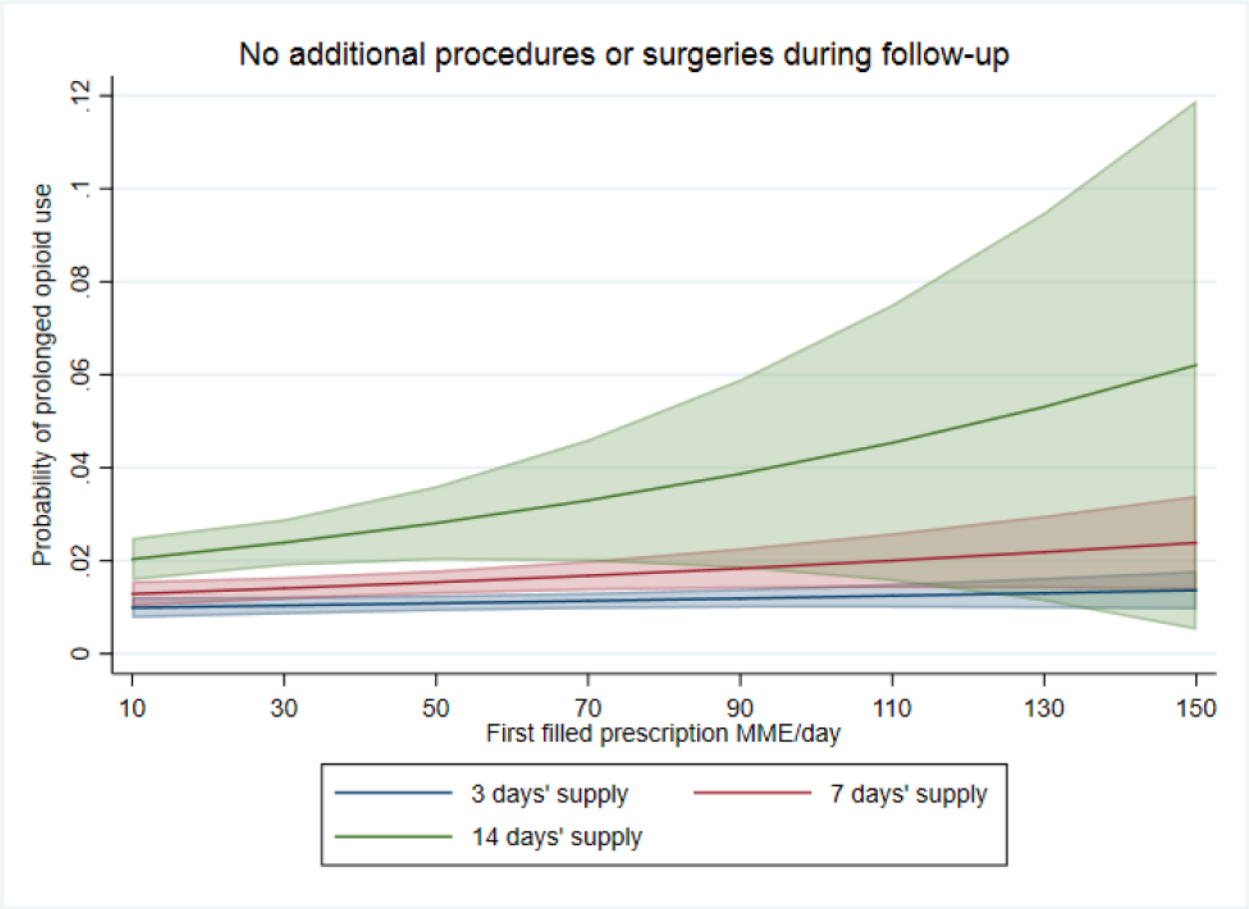
5-H-2: Emergency care subgroup only (n= 10,336)



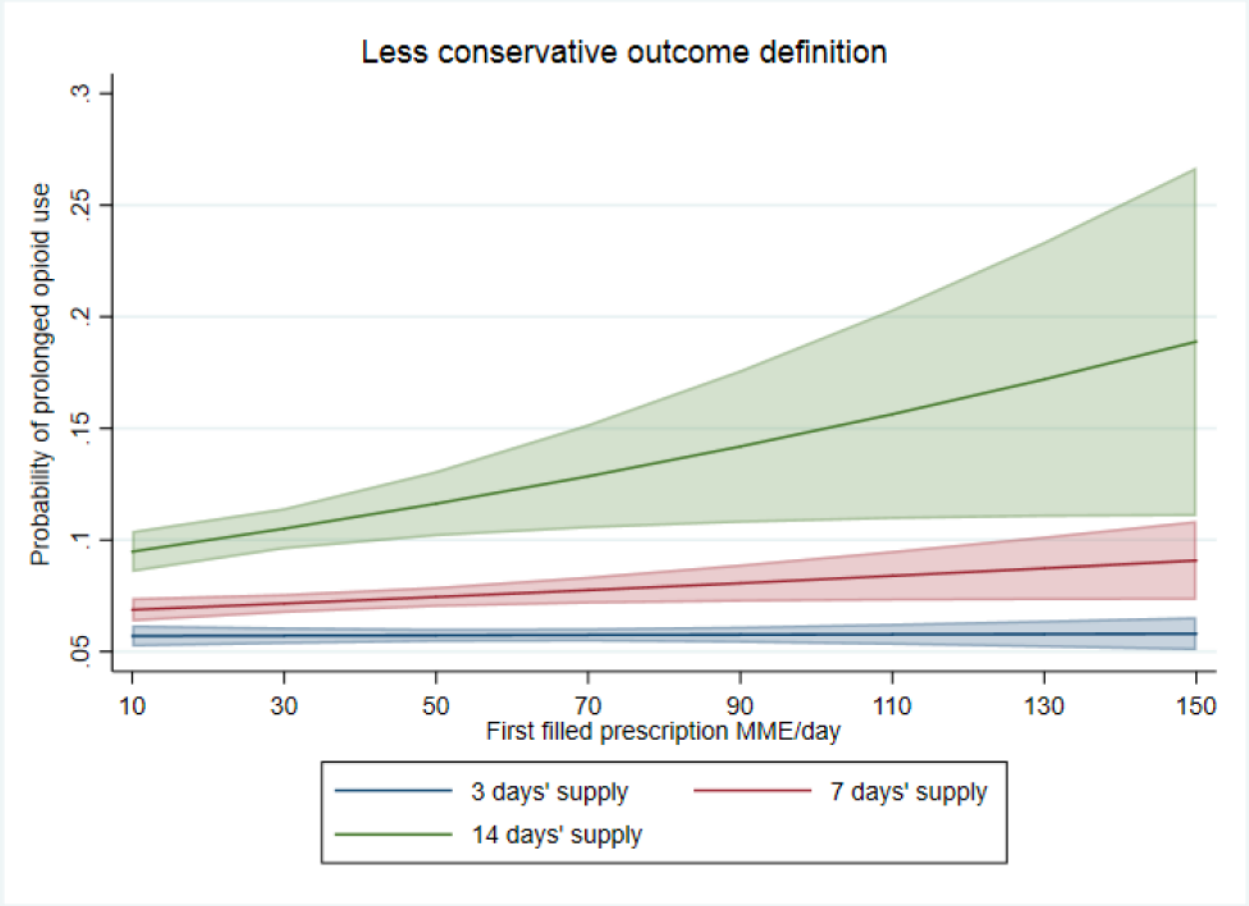
5-H-3: No history of cancer diagnosis in previous year subgroup (n= 23,832)



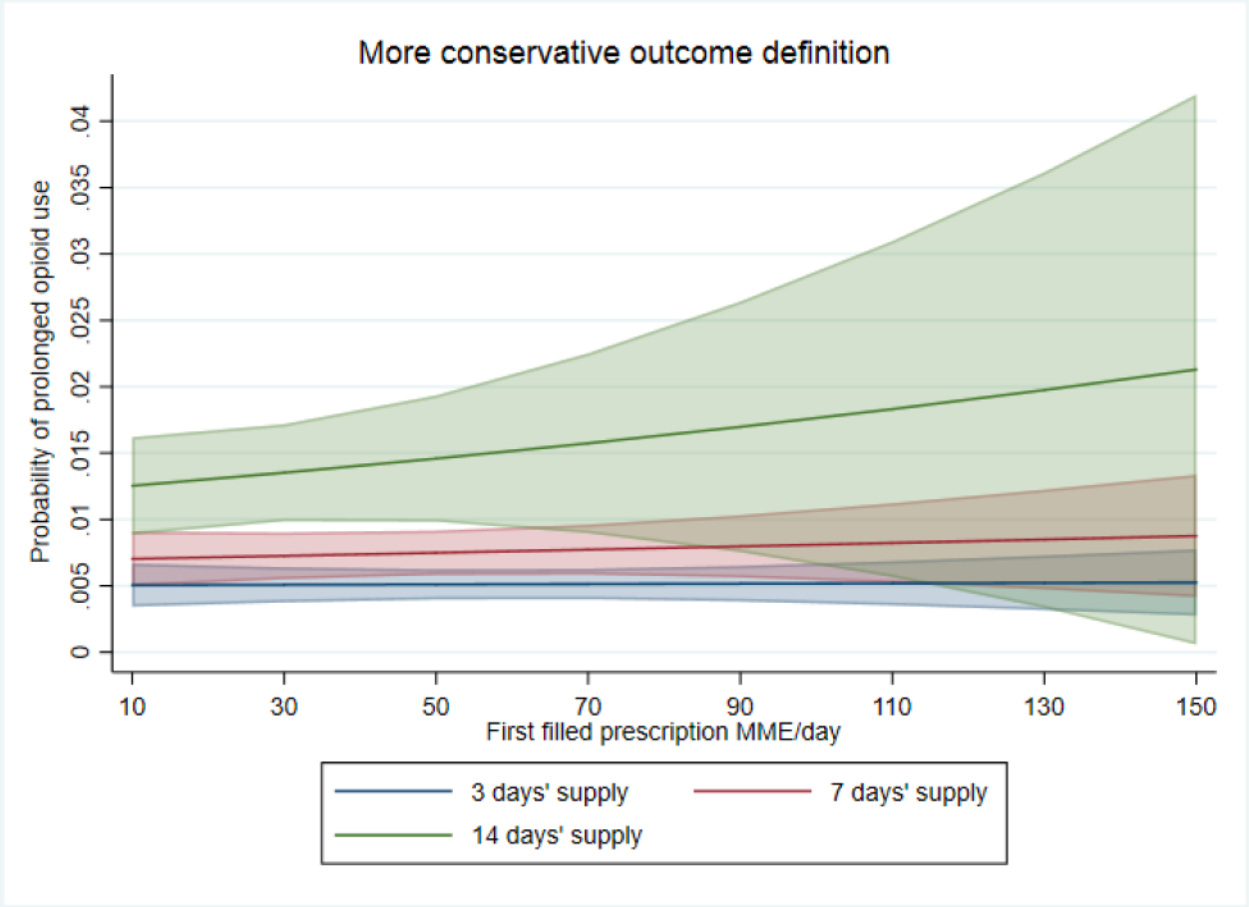
5-H-4: No additional procedures during follow up subgroup (n= 18,314)



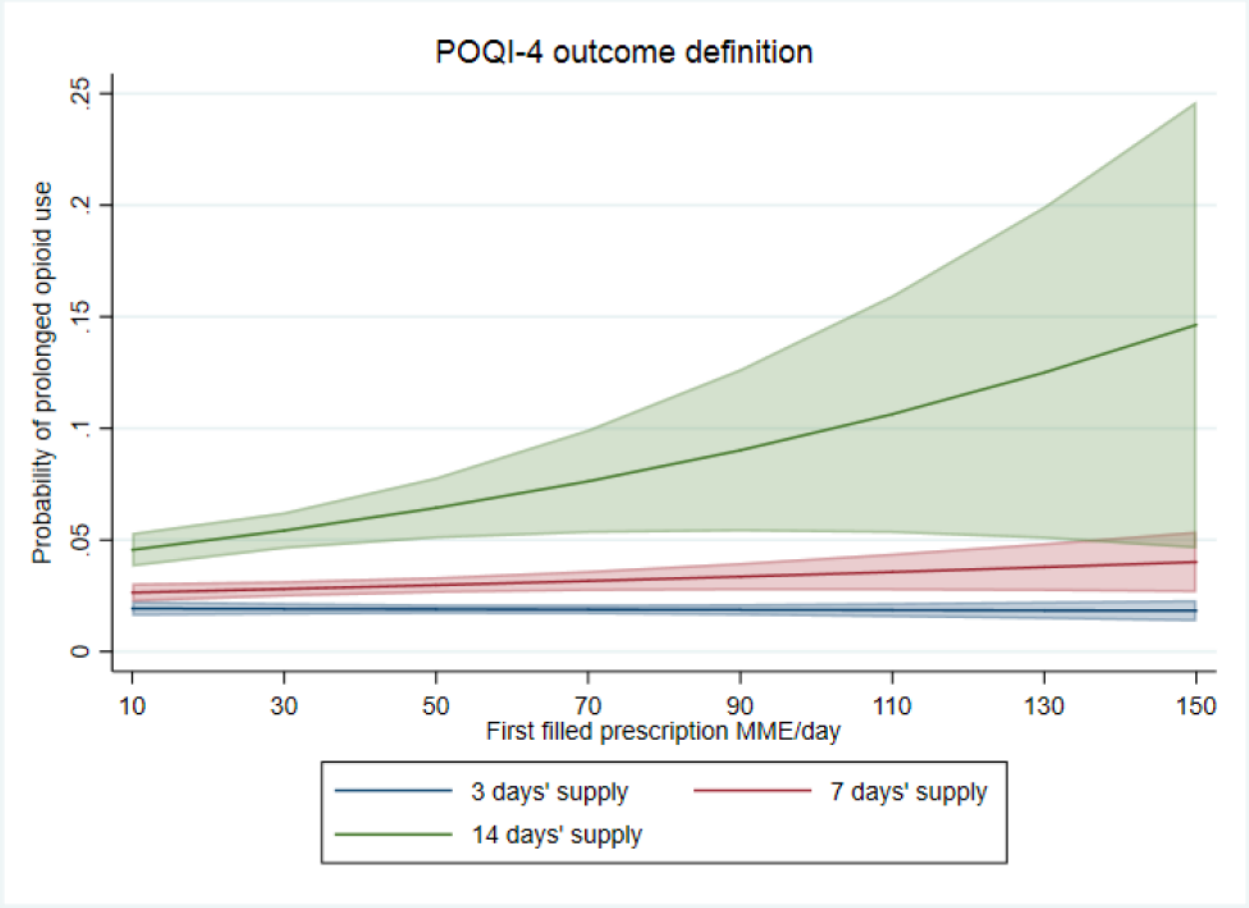
5-H-5: Less conservative outcome definition [≥ 1 fill in 91 to 180 days from index date] (n= 27,665)



5-H-6: More conservative outcome definition [≥ 4 fills with at least one in each of 8 to 90; 91 to 180; 181 to 270; 271 to 365 days] (n= 18,525)



5-H-7: POQI-4 outcome definition [≥ 1 fill in 91 to 365 days, with at least 60 days' supply] (n=18,525)



6 Chapter Six: Discussion

6.1 Note to reader

In this chapter, I summarize the findings of the three studies included in this thesis, present strengths and limitations, discuss potential implications for clinical and policy decision making, and suggest avenues for future research. More in-depth discussions of thesis study results are presented in their respective chapters.

6.2 Summary of findings

6.2.1 Overall summary

In this thesis, I investigated opioid prescribing patterns and prolonged opioid use in opioid naive patients following surgical and emergency care in the province of Nova Scotia. I set three distinct but connected objectives to (1) estimate risk of prolonged opioid use globally and identify important risk factors, (2) explore prescribing patterns locally and how they may differ across settings and provider specialty, and (3) estimate risk of prolonged opioid use locally and determined how risk may differ by prescribing patters. I achieved the three thesis objectives by conducting three distinct studies using various epidemiological methods including systematic review, meta-analysis, and assessment of overall certainty in evidence; and designing a cross-sectional study and cohort study using population-level linked databases and using descriptive and inferential analytic techniques to analyze and report findings. To provide a comprehensive view of use patterns, patient characteristics, and settings of care in the two primary studies included in this thesis, two novel datasets were created for the thesis using linked population-level data sources.

For the first aim, by synthesizing existing evidence, I identified patient demographic and clinical characteristics that are associated with higher risk of prolonged use and systematically assessed the trustworthiness of evidence for each characteristic. This is the first review that has included patients across surgical, emergency, and dental care settings and has quantitatively summarized data about risk of prolonged use and important risk factors and assessed certainty in evidence. The findings from this review give a comprehensive view of the state of evidence in this area – albeit the search needs to be updated at the time of thesis completion.

For the second aim, I documented patterns of prescribing to this patient population in Nova Scotia and found that while the majority of prescriptions were not long in days' supply or high in dose, almost one quarter of patients in surgical care had filled high-dose prescriptions and almost one-fifth of those in emergency care filled prescriptions longer than seven days' supply. I also found that patterns of prescribing differed across surgical subspecialties, suggesting further exploration is warranted to understand these patterns and mitigate unnecessary risk when appropriate. To my knowledge, this is the most comprehensive description of patterns of prescribing to opioid naive populations in Nova Scotia.

For the third aim, I found that prolonged opioid use is a rare but existing outcome of opioid prescribing to opioid naive patients in surgical and emergency care settings in Nova Scotia. This finding expands our understanding of the scope of this problem in Nova Scotia as prolonged opioid use has only been reported for a population of patients presenting to emergency departments with low back pain, but to my knowledge, no other populations have been assessed for this outcome in the province. I also showed that while

risk is small overall, it differs by patterns of prescribing even after adjusting for important confounders. Namely, I found that high dose prescribing is associated with increased risk of prolonged use when prescriptions are long but not short in days' supply. This latter finding expands our understanding about how prescribing patterns related to risk of prolonged use in opioid naive populations.

Collectively, this thesis advances our understanding of opioid prescribing patterns and outcomes in opioid naive populations treated with opioids for acute pain. This thesis provides evidence that may be perceived as useful for various stakeholders including physicians, patients; public health professionals, medical specialty bodies, guideline developers, and policymakers.

6.2.2 Summary by Aim

In **Chapter 2**, I identified 35 studies that assessed the risk for prolonged opioid use as well as risk factors of prolonged opioid use in opioid-naive populations who filled opioid prescriptions for acute pain or after receiving care in the acute care setting. These studies were identified after a systematic search of five databases from inception until April 29, 2019. Since that date, the number of studies in this area grew, and an updated search would yield more studies to be included, of which at least three would be Canadian studies.

I summarized the findings in included studies and considered the possibility of bias using tools that were developed for studies estimating overall risk of outcomes in defined patient populations[1], and tools that were developed for studies assessing associations between risk factors or prognostic factors and outcomes in observational studies[2]. I also assessed overall certainty in available evidence using modified GRADE

criteria[1,3], and I conducted assessments that were specific to overall risk of the outcome and to each assessed risk factor independently.

The review included more than 2 million surgical patients, 1.2 million patients with injury and/or who received emergency care, and more than 75,000 patients with dental pain across the 35 studies. I found that risk of prolonged opioid use, on average, was 6% after surgical care, 9% after injury or emergency care, and 3% after dental care. Risk varied across surgical subspecialties, from 0% to 16%. In the injury/emergency care group, risk differed based on whether surgery was also performed (16% if yes and 5% if no). I also found that risk was lower when prolonged opioid use was measured at long-term follow-up (i.e., beyond 180 days from baseline) compared to intermediate-term follow-up (i.e., 60 to 180 days from baseline). In the surgical group, risk was 8% at 60 to 180 days and 4% beyond 180 days; in the emergency/injury group, risk of prolonged opioid use was 11% at 60 to 180 days and 7% beyond 180 days.

Using the same systematic methodology, I was able to identify at-risk groups for prolonged opioid use. I found high-certainty evidence that Black race and ethnicity, presence of co-morbidities as measured using co-morbidity indices, and having a history of arthritis, a history of anxiety, a history of depression, or a history of illicit drug use at baseline were all associated with a potentially clinically important higher risk of prolonged opioid use. I also found moderate-certainty evidence that having a history of back pain, a history of neck pain, a history of tobacco use, or a history of alcohol use were also associated with a higher risk of prolonged use.

I found that there are few studies about first-prescription factors, which limited my ability to draw conclusions about the association between most first-prescription

factors and prolonged opioid use. Based on a narrative, not quantitative, synthesis of available evidence, I found that long-acting formulations (as opposed to short-acting) and tramadol (compared to non-tramadol opioid alternatives) were associated with a higher risk of prolonged opioid use, and the evidence was assessed to be of moderate-certainty. A lack of association between first-prescription days' supply and average daily dose was not conclusive, as the evidence was very limited and was collectively assessed to be of 'low' and 'very low' certainty, respectively. I also found that when measures of cumulative opioid dose (i.e., measured as total MME of first-prescription, or total perioperative MME) were considered, a higher risk of prolonged use was observed with higher cumulative dose. However, due to study limitations, inconsistency across studies, and perceived potential for publication bias, the evidence was collectively assessed to be of very low certainty.

In **Chapter 4**, I used linked administrative databases to obtain a population-level view of opioid prescribing patterns to opioid-naive patients who filled opioid prescriptions after receiving surgical or emergency care in Nova Scotia between April 2017 and March 2019. I also determined how frequently prescriptions of >7 days' supply, ≥90 MME/day, or for long-acting formulations, were filled by this population. Finally, I assessed whether these prescribing patterns differed across settings, for the subgroup that received surgical care, and across provider specialty groups.

The results of the analyses are described in Chapter 4. Briefly, I found that, on average, prescriptions were written for 3 days (IQR 2 – 5) and 50 MME/day (IQR 30 – 75), and that one-half (50.0%) of this opioid-naive population had filled hydromorphone formulations, while one-quarter (26.4%) filled codeine formulations, and less than 10%

each had filled tramadol, morphine, or oxycodone formulations. Furthermore, 10.9% of subjects had filled prescriptions that were >7 days' supply and 20.2% filled prescriptions that were ≥90 MME/day, while <1% filled prescriptions for long-acting opioid formulations.

In the analysis assessing potential variation across settings, I found that those who filled prescriptions after emergency care were twice as likely to have prescriptions >7 days' supply, but less than half as likely to have ≥90 MME/day compared to those who filled prescriptions after surgical care. For those who had surgical care, with or without emergency care, I reported potentially important variations in prescribing patterns across provider specialty groups, even after adjusting for type of procedure performed and a set of patient characteristics that may influence physicians' prescribing decisions. Those who filled prescriptions after having a procedure billed by an otolaryngologist had the highest proportion of filling first-prescriptions of long duration (14.8%), exceeded only by those who had procedures performed by non-surgical, non-general practice specialties (i.e., internal medicine and radiology). However, the latter group accounted for only 1% of the entire surgical population. Also, I found that 39% of those who had procedures billed by orthopedic surgeons had filled prescriptions ≥90 MME/day – the highest proportion among all specialties. These patterns were observed even after adjusting for procedure type and patient characteristics, although more granular adjustment for procedure and pain type may be warranted.

In **Chapter 5**, I built on the information gained from the systematic review regarding the limited evidence available on first-prescription factors and risk of prolonged opioid use. Because prescribing patterns are modifiable during the clinical

encounter, I assessed this to be an important area to address and to add to the literature. I also used the information obtained about important risk factors to inform the choice of covariates to include in the analysis. I used the same cohort analyzed in Chapter 4 and retrospectively followed them for six months (180 days) after the opioid prescription was filled at baseline. I applied additional exclusions to the cohort to account for the methodological needs of a cohort study, the most important of which was ensuring each included subject had at least 180 days of follow-up data. I assessed the overall risk of prolonged opioid use in this local cohort using a main and alternative definitions. I determined whether first-prescription average daily dose, days' supply, and type of formulation (long- versus short-acting) were associated with higher risk of prolonged use after adjusting for important covariates that are known to be associated with a higher risk of prolonged use. I also assessed whether the risk associated with average daily dose differed by days' supply (i.e., whether an interaction existed).

In this study, I found that 3.5% of those who were opioid naive and had filled opioid prescriptions after surgical or emergency care became prolonged opioid users. Prescriptions with greater days' supply and long-acting formulations were associated with a greater risk of prolonged opioid use – findings that concur with the more recent studies conducted in this area. I also found that, while the overall association between average daily dose and prolonged use was weak, risk differed in important ways across days' supply values. For the same opioid dose, risk of prolonged use increased substantially as prescriptions became longer in duration. Furthermore, I found that at 3 days' supply, increasing the average daily dose increased the risk of prolonged use minimally, with statistical testing showing no difference from 'no change'. However, a

higher risk of prolonged use was observed at 7 and 14 days' supply as dose increased. These findings agree with previous studies that found higher *total* MME of first filled prescription, likely a function of daily dose and days' supply combined, to be associated with higher risk of prolonged use. [4-9] My study's findings expanded on how this risk may manifest itself across various daily dose and days' supply combinations, making the results more relevant and accessible for those in clinical practice.

6.3 Strengths and Limitations

In this thesis, I used a sequential process to determining priorities for investigation in the area of opioid prescribing to opioid naive patients presenting to acute care settings and/or with acute pain. I started with identifying prolonged opioid use as an outcome of interest and reviewed all available evidence systematically to determine how common the outcome is and what factors may be important risk-factors. In the systematic review, I identified prescribing patterns to be an area with deficient evidence and also found that evidence from Canada about this phenomenon is very limited. I subsequently designed a study to determine the extent to which this phenomenon exists locally and designed an analysis that would explore associations between prescribing patterns and risk of prolonged use that addressed the limitations in existing evidence. I further explored prescribing patterns and the prevalence of prescribing in long days' supply and high-dose, two patterns of prescribing that the evidence suggested may be associated with higher risk of harms. This iterative process allowed me to prioritize areas of study strategically based on gaps in evidence and take into account important co-variates in the analysis.

The thesis studies used rigorous methodologies in both evidence synthesis and primary studies that are recommended for use when studying opioid safety. The systematic review focused exclusively on opioid naive populations across three of the largest settings in which opioids are routinely prescribed for acute pain in Canada namely: surgical, emergency, and dental settings. Evidence included the review was derived from large, longitudinal databases with objective and complete outcome measures, and risk of bias assessment and assessment of overall certainty in evidence was conducted for each risk factors evaluated for a detailed, transparent, and reliable assessment of each included factor.

This thesis provides the first comprehensive piece of evidence about opioid prescribing patterns to opioid naive populations in surgical and emergency care settings in Nova Scotia and related outcomes. The primary studies relied on population-level cross-sectional and cohort study designs and utilized population-level data sources and linkages across these sources. Further, the studies relied on measures of outcomes that were objective based on documented filled opioid prescriptions. All of these design and analysis elements are recommended when researching prescription opioid safety,[10] and increase the validity of findings.

This thesis has limitations in relation to the systematic review search date and potential heterogeneity, primary studies cohort selection and co-variate measurement, and conceptualizing the outcome prolonged opioid use and underlying assumptions.

In relation to the systematic review evidence (Objective 1), the search date ended in 2019. Evidence had grown since then and re-running the search will likely identify additional studies to be included in the review. This might influence review findings; I

expect that there will be sufficient evidence about prescribing factors to pool results and quantitatively synthesize the evidence, and that analysis of patient characteristics will produce more precise estimates and higher ratings of certainty in evidence for some of the factors. I also note high I^2 values and evidence of potential clinical heterogeneity in some of the meta-analyses presented in this study challenging the appropriateness of the decision to pool across included populations. This is particularly important for meta-analyses of risk, as assessment of event rates is most meaningful when summarized for populations that are homogenous enough to closely represent the target population. It has been recommended however not to rely on high I^2 values as evidence of important heterogeneity in meta-analyses of primary studies that include large databases as estimates of event rates are often highly precise due to the large sample size included, leading to potentially misleading high I^2. For clinical heterogeneity, I anticipated that in surgical populations heterogeneity by subspecialty may be present and planned subgroup analysis a-priori that showed notable variation. Perhaps presentation of results by subgroup only may be more meaningful in this population. I also anticipated that in the injury/ED-presenting pain population, heterogeneity may exist that may be explained by whether the population included surgery for trauma - potentially a marker of severity of injury/trauma. Again, I found in a pre-planned subgroup analysis notable variation across the subgroups. There is reason to consider whether other meaningful subgroups exist for this population, as pain presenting to the ED can widely vary. While we took a broad view of populations in this review, it might be more meaningful to keep populations separate and avoid pooling them together in future studies for better understanding of risk across included populations.

There are limitations that pertain to cohort selection and co-variate measurement in the thesis primary studies (Objectives 2 and 3) - these limitations are all connected to the secondary nature of the data sources utilized for these Objectives. While routinely collected administrative secondary data sources provide a comprehensive view of populations of interest and their health outcomes, and may be ideal for ascertaining outcomes like drug filling, they have been collected primarily for administrative purposes and therefore often miss information that researchers may find relevant in their studies, and this thesis is no exception.

First, the definition of opioid naivety depended on the absence of recorded prescription opioid filling, similar to many other studies utilizing drug claims databases.[9,11-16] Because the included drug use data source does not capture opioid use outside of prescription filling in community pharmacies, we may have misclassified the naivety status of some study subjects who used opioids obtained from the hospital, through diversion (e.g., through family or friends), or from the illicitly manufactured market. These misclassified subjects may have been erroneously included in the cohorts of **Objectives 2 and 3**. This limitation may have manifested itself in the results of **Objective 2** by potentially demonstrating a higher prevalence of high-dose prescriptions, long-days' supply, and long-acting formulation prescriptions than had actually occurred for the truly opioid-naive population. Physicians may have had additional information regarding opioid use status during the clinical encounter that would have explained their prescribing higher doses, for longer days, or long-acting formulations. The outcome most likely to have been influenced by the potential misclassification of opioid status was

filling prescriptions for long-acting formulations, which was observed in <1% of the study population, as discussed in **Chapter 4**.

In **Objective 3**, the inclusion of some non-opioid-naive subjects may have potentially overestimated the overall risk of prolonged opioid use for the entire population. as previous non-naivety is an established strong risk factor for prolonged opioid use in patients treated with opioids for acute pain.[17,18] It may have also manifested itself in the observed association between higher-dose and longer days' supply prescriptions and higher risk of prolonged use. If most of the subjects who received these prescriptions were non-naive at baseline, then it is possible that their non-naivety, rather than dose or days' supply of their prescription, was what affected the risk of prolonged use.

The second limitation related to the use of secondary data sources which lack information about psychometric properties of measures of comorbidities (i.e., patient clinical characteristics) leaving gaps in our assessment of accuracy and reliability of these measures, with the potential for misclassification. In **Objectives 2 and 3**, patient comorbidities were included as covariates in the analysis. Any misclassification in these factors may have introduced residual confounding. However, because the same settings and methods of measurement were used for all subjects included in the studies, and data about comorbidities were complete through exclusion of those with interrupted enrolment or <12 months of enrolment in the year preceding the first-filled prescription, these measurement limitations should not lead to differential misclassification, and the impact on findings should be minimal.

There are also limitations pertaining to the analysis of Objective 2 that must be noted. Lack of adjustment for provider characteristics that have been shown to be associated with prescribing behaviours may have biased results by introducing unmeasured confounding. These characteristics may vary across specialty groups in important and systematic ways and adjusting for them in the analysis would have been important for more accurate estimation of association between specialty and outcomes. Data about prescriber place of training and years since graduation was present for about three-quarters of included subjects. Incorporating such information by adding a 'missing data' category for these variables rather than excluding them from the analysis could strengthen study findings. Another limitation to point out is that average associations between specialty and prescribing outcomes may conceal important variation within groups. There may be important variation by providers within each specialty that needs to be explored. Adding a random effects function by provider ID to the regression analysis models can be one way to address this limitation.

Another limitation pertains to the assumption that prolonged opioid use, the outcome assesses in Objective 3, was not intended at baseline for all included study subjects. Because we do not have information about prescriber or patient intentions or expectations regarding the intended duration of opioid use, we cannot know with absolute certainty that initiation for long-term opioid use was not intended from the start. Including opioid prescription fills within 14 days of surgical or emergency care introduces a possibility that some subjects received their prescriptions from subsequent visits to other settings, including primary care, for example. Opioid initiation for long-term use in those settings could be expected for some patients. To gain more insight

about average time from care to prescription fill, I analyzed available data that measured time in days from emergency department visit to prescription opioid fill. In the emergency care group, median (IQR) time was 1 day (0 – 2), and for those who received emergency plus surgical care, it was 3 days (1 – 6), indicating the likelihood that filled prescriptions originated from surgical and emergency care settings was high for the majority of included subjects.

Importantly, there may be limitations to the definition of prolonged opioid use that need to be considered. The main definition used in Objective 3 might not have adequately differentiated between continuous opioid use and having filled multiple additional short-supply prescriptions of opioids during the follow up period. We employed a few strategies to overcome this limitation. In the primary definition, we required one or more prescriptions to have been filled in the period from 8 to 90 days of follow up to increase the chance that fills beyond 90 days are not separate events. We also conducted sensitivity analyses in which we excluded those with additional procedures during follow up which could be separate indications for opioid use. We also used two alternative definitions of prolonged use that captured higher frequency of filling, one requiring at least four additional fills during one year of follow up of which at least one must have occurred during each of the follow up quarters, and another that required at least 60 days' supply. However, previous work suggests that these measures might still be inadequate in capturing continuous use and that there are better alternatives such as measuring use that spans a minimum of 90 days and includes a minimum of 120 days' supply or 10 or more fills.[4]

6.4 Implications

Findings from the three studies included in this thesis collectively indicate there may be opportunities to improve the safety of opioid prescribing to opioid-naive populations being treated for acute pain, or more broadly, in the acute care setting. Results may be useful for various stakeholders including guideline developers, policymakers, medical specialty bodies, public health professionals, physicians who treat adults for acute pain, and patients and their families.

Guideline developers searching for evidence to inform the creation of recommendations about opioid prescribing for opioid naive patients presenting to the surgical or emergency care setting may find the results in this thesis identifying important risk factors useful for determining at-risk groups for prolonged use. They may also find the estimated risks associated with various prescribing patterns useful for determining safer prescribing practices.

Findings about risk of prolonged opioid use may be useful for physicians who take care of patients who are previously opioid naive and presenting with acute pain for which opioids are being considered, such as surgeons across all subspecialties, emergency care doctors, and dentists. Results may also be of relevance to patients and their families, who may wish to weigh the risk of prolonged opioid use associated with receiving a first opioid prescription and balance it against opioid benefits and/or compare the benefit-risk profile with other alternative therapies.

Based on the findings from **Objective 1** indicating that there is moderate- to high-certainty evidence that some patient characteristics at baseline are associated with a potentially clinically important higher risk of prolonged opioid use, risk stratification

approaches may be used to support safer prescribing of opioids. Some of these factors, including a history of psychiatric illness or substance abuse are already being used to stratify patients who are being considered for opioid therapy for chronic pain.[19,20] Findings from this thesis suggest there may be opportunities for similar risk stratification approaches when opioids are being considered for acute pain treatment in opioid-naive populations. When patients are assessed to have one or more of the characteristics associated with a higher risk of prolonged use, physicians can have discussions with them about balancing the benefits and risks and suggest non-opioid alternatives. Alternatively, risk stratification may benefit those whose risk of prolonged use is deemed low or very low by deterring their physicians from withholding opioids when they can be safe and effective.

Based on findings in Objective 1, some factors that can be considered include a history of anxiety or depression, a history of drug or alcohol abuse, a history of tobacco use, a history of multiple co-morbidities, and a history of chronic pain including arthritis, back pain, and neck pain. Patients with pre-existing or recent history of chronic pain may need to be referred for further assessment by their primary care physicians or pain medicine specialists before additional refills are given. Objective 1 results also suggest that prescriptions originating from emergency departments and/or for injury-related pain should be expected to results in higher baseline risk of prolonged use compared to prescriptions related to surgery or dental-related pain. Objective 3 results also suggest that when opioids are prescribed for acute pain in opioid naive patients, prescriptions should be for short-acting formulations and short in duration, as suggested by the US CDC guideline for prescribing for acute pain in the primary care setting.[19] Findings also

suggest that when high-dose prescribing is deemed necessary, to keep prescriptions as short as possible to minimize risk of prolonged use.

For all of the issues discussed above, it is important to point out that an assessment of all existing evidence about other opioid harms and benefits, and consideration of patients' values and preferences is essential before recommendations for clinical practice are made. These domains can be considered systematically using existing frameworks that have been developed to assist with moving from evidence to recommendations and decision-making.[21]

Another important issue to consider is that not all risk factors can be treated equally (i.e., used in the same manner to influence clinical decision making). While there may be physiological or biological explanations to link having a history of psychiatric illness or substance use to prolonged use, the risk factor Black race, identified in **Objective 1** as an important risk factor, does not. Rather, the higher risk of prolonged opioid use associated with being Black may be due to underlying mechanisms such as systemic racism and unconscious bias against individuals from these groups, leading to the myriad of poor outcomes observed across various healthcare settings.[22,23] Attempts to stratify individuals by race without inspection of root causes may further exacerbate already existing prejudices against certain groups in relation to pain management.[23] Similarly, a history of chronic pain conditions was found to be associated with higher risk of prolonged use. However, if patients with these conditions are found to benefit from using opioids for pain relief, then rather than withholding opioids from them to treat acute pain in fear of risk of unintended prolonged use, treating physicians may wish to refer them to pain medicine specialists for follow-up, or advise their primary care doctors

to do so, prior to any refills being written. Overall, I suggest that a thoughtful approach to interpreting what a "risk factor" entails is necessary when such factors are being considered for risk stratification and similar approaches to tailoring care delivery.

Policymakers who may want to gain greater understanding of current prescribing patterns and how they compare to current guidelines, or those who wish to find opportunities to create policies that promote safer prescribing to opioid naive populations presenting to acute care setting may also find parts of the evidence presented in this thesis useful. Results from **Objective 2** showing that 10.9% of filled prescriptions were longer than one week's supply, 20.2% of filled prescriptions were ≥90 MME/day, and the average prescription was 50 MME/day suggest that there may be opportunities for improving opioid prescribing patterns. Results also showed that prescribing >7 days' supply and ≥90 MME/day varied across clinical settings and prescriber specialties. This suggests that specific settings or specialty groups can be prioritized to conduct evaluations to explore explanations for the observed prescribing patterns and, if appropriate, to improve prescribing through interventions or quality improvement initiatives. For example, 16.9% of those who filled prescriptions after emergency care and 14.8% of those who filled prescriptions after a procedure billed by an otolaryngologist had prescriptions >7 days' supply. Current Canadian guidelines for acute pain, although not focused on surgical or emergency related pain, recommend that opioid prescribing is for 3 days or less, and that 7 days is rarely indicated.[24,25] Recent evidence[14,16,26], as well as findings from **Objective 3** demonstrate that the risk of prolonged use is greater with longer days' supply prescriptions. Therefore, these settings can be prioritized for exploring appropriateness and drivers of these prescribing patters.

Medical specialty bodies may wish to self-evaluate prescribing patterns and their specialty's potential contribution to unintended prolonged opioid use in previously opioid naive populations being prescribed opioids for acute pain. Across the United States and Canada, calls have been made for the critical evaluation of prescribing practices overall[27], and within specialty groups and settings, including in otolaryngology[28], and the emergency department.[29] Before considering most prescriptions longer than 7 days duration or higher than 50 to 90 MME/day excessive, it is important to explore what motivates these prescribing patterns in future studies or through quality improvement initiatives, and then decide whether interventions to modify prescribing behaviours are necessary. Patients' needs may differ enough across these settings to account for the observed variations, however, prescribing cultures and conventions within settings and specialty groups may also explain these findings. If intervention is found to be necessary, evidence has shown that opioid stewardship programs can be effective in driving down discharge opioid dose and quantity, without changes in pain or need for refills compared to before intervention implementation.[30]

Based on findings from this thesis, collectively, specific potential local policy interventions could include creating quality improvement initiatives that can monitor prescribing patterns and outcomes including prolonged use for this population and promote internal evaluation of clinical indications for prescribing in excess of certain thresholds – the College of Physicians and Surgeons of Nova Scotia in its 2020 professional standards regarding initiating opioids for acute pain already requires documentation of clinical circumstances surrounding prescribing in excess of seven days.[31] Strict prescribing limits should not be set by policymakers as these policies can

cause unintended harm and experts have recommended against this kind of appoach.[32] Rather, specialty bodies can embark on evaluating their specific patient needs and commission guideline developers to produce tailored guidelines for their population(s).

For medical specialty bodies I suggest that based on findings from Objective 2 that surgical specialties with a high prevalence of high-dose prescribing may evaluate average days' supplied for these prescriptions and determine whether all high-dose prescriptions are necessary for patients receiving them and emergency medicine specialty review patterns of prescribing in emergency departments to ensure that long-days' supply prescriptions are clinically justified for patients who are receiving them and if not, exploring drivers of these patterns of prescribing.

Specific findings from this thesis may also be of relevance to public health professionals who may find quantifying the absolute risk of prolonged use in this population helpful for planning and/or creating interventions to prevent unintended transitions. From a public health perspective, it is important to consider how prescribing patterns might influence exposure levels for populations. Proportions provide insight, but absolute numbers communicate a more important message. While the majority of patients in **Objective 2** had prescriptions that were ≤7 days' supply and <90 MME/day, just under 4,000 opioid-naive individuals were exposed to first prescriptions >7 days' supply, and about 7,300 opioid-naive individuals were exposed to doses ≥90 MME/day within the two-year study period. Keeping other factors such as patient clinical profiles, demand, and the care delivery and regulatory environment constant, opioid prescribing that follows the same patterns would result in 12,000 opioid-naive patients exposed to first prescriptions >7 days' supply and 22,000 exposed to ≥90 MME/day over six years. An

expansion in exposure also expands associated risks, and even for rare risks, absolute numbers will rise in the population. This public health perspective may be taken into account when the risks and benefits of opioid prescribing patterns are weighed.

Similar to the argument made above, findings from **Objective 3** show that in absolute numbers, thousands of patients can be expected to become prolonged opioid users after first exposure after surgical or emergency care in Nova Scotia. In the six months following their first filled prescription, 3.5% of the included population, or 965 individuals became prolonged opioid users. Over many years this number will continue to grow as more opioid-naive patients fill opioid prescriptions after surgical and emergency care, and the risks associated with long-term opioid therapy, even when rare, will become more prevalent in the community.

6.5 Future research

Multiple avenues of research can be pursued to move forward our understanding of safe opioid prescribing for opioid-naive patients with acute pain, or in the acute care setting more broadly. Priority areas that emerged from this thesis work are: 1. exploring whether prolonged opioid use in opioid naive populations being treated for acute pain is unintended, and 2. unpacking what the construct prolonged opioid use is measuring, and how it correlates with other important opioid-related harms.

An important question arising from this thesis is whether prolonged opioid use is always unintended at baseline? Researchers could conduct mixed-methods studies to obtain qualitative information from physicians and patients to gain important insights. Physicians can be interviewed about their intention for long-term initiation of opioids, and their general expectations for duration of use. Patients with prolonged use could be

asked about their motivation for use, and whether the expectation at baseline was that they would be on opioids for many months following the sentinel event. As previously discussed, based on existing evidence, there are reasons to believe that, regardless of whether prolonged opioid use was unintended at baseline, prescription opioid use initiated in the acute care setting that becomes prolonged is unfavourable and may potentially contribute to a higher risk of harms compared to initiation in primary care or pain medicine settings. As discussed in Chapter 1, long-term opioid therapy is associated with a myriad of adverse events and opioid-related harms.[33] To avoid such harms, prolonged opioid use should be reserved for patients who are carefully selected[19,20], and that treatment agreements and long-term monitoring plans should be established.[19] When opioids are prescribed in the acute care setting, the extent to which these considerations are taken into account is unclear, given the nature of the acute care setting and the limited opportunity for regular follow-up. When these treatment plans and agreements are bypassed at initiation, patients may be exposed to even higher risks of harm than would be expected for chronic pain patients who initiated long-term opioid therapy in long-term care settings. Still, gaining a better understanding about whether prolonged use is unintended at baseline will be an important first step in decreasing transitions to prolonged use from prescribing in acute care settings for acute pain.

Another important question emerging from this thesis is what prolonged opioid use is actually measuring: is it use for ongoing or pre-existing chronic pain, use by the patient for other non-pain related reasons (i.e., what was formerly labeled misuse or abuse), use due to a developed physical dependence or tolerance, or an incident opioid use disorder? There are data supporting each of these possible explanations, suggesting

that prolonged use may be measuring different things for different people with the same measured outcome. Results from **Objective 1 (Chapter 2)** demonstrate that a history of chronic pain is associated with a higher risk of prolonged use, suggesting that continued opioid use to treat an underlying chronic pain condition may be one possibility. Delgado et al. found that many of the opioid-naive patients who received opioid prescriptions after a visit to the emergency department for an ankle sprain and continued to use them beyond the short-term period did so for unrelated pain conditions.[34]

Opioid misuse, abuse, or an opioid use disorder may be another explanation for observed prolonged use in some patients. Some of the risk factors for prolonged use identified in Objective 1 including anxiety, depression, and substance use are also identified as risk factors for opioid misuse[35] and opioid use disorder[36], suggesting that prolonged use may be measuring misuse or an opioid use disorder in some patients who transitioned to prolonged use. Further, opioid use disorder is defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* as *"*A problematic pattern of opioid use leading to clinically significant impairment and distress, as manifested by at least 2 of 11 diagnostic criteria presented in the DSM-5 manual, and occurring within a 12-month period" [37]. The first criterion states that "Opioids are often taken in larger amounts or over a longer period of time than intended." Development of an opioid use disorder should therefore be considered as a possibility when evaluating possible explanations for prolonged use. Bicket et al. recently provided similar reflections and suggested that this possibility should be considered in patients who transition to prolonged opioid use after surgery.[38]

There are opportunities for deeper understanding of the potentially distinct opioid use journeys of patients after a first prescription for acute pain. Patient trajectories may depend on multiple factors including evolution of pain itself as well as propensity for misuse. Expanding on potentially distinct pathways will likely help us better understand the phenomenon of prolonged opioid use, support the development of tailored recommendations for heterogenous groups of patients, and avoid causing undue restrictions on opioids when they have the potential to be helpful and safely used by some patients.

It is important to note that some experts will challenge the notion that prolonged use is in itself an inherently poor outcome across all patient groups. It is suggested that prolonged opioid use is only a problem when it *is* a problem either due to misuse and associated harms or for representing an underlying opioid use disorder. Use is perceived to be appropriate when prolonged use represents continued use that effectively manages pain which has evolved into chronic pain after the acute pain event. Because the dataset used in the current work doesn't have information about indications for additional opioid use during follow up or data about indicators of problematic use or the development of an opioid use disorder, there are limitations in current understanding of what proportion of patients with prolonged use may fall into this category.

In studying the outcomes of opioid prescribing, researchers may supplement current knowledge about prolonged opioid use with additional data about other opioid-related harms that are important to patients. These might include incidence of overdose, hospitalization for opioid-related harms, a recorded opioid use disorder, or death from opioid-related toxicity. Researchers may additionally wish to analyze the relationship

between prolonged opioid use and these outcomes to expand our understanding about the consequences of prolonged use, and associated patient-important outcomes.[38]

Other areas that can be explored to expand our understanding of opioid prescribing safety and contribution of prescriber characteristics include: 1. Determining patterns of prescribing stratified by clinical pain diagnosis and exploring variation by prescriber characteristics within those groups 2. Exploring prescriber motives for prescribing practices 3. Exploring other indicators of prescribing safety.

To increase the relevance of research findings about prescribing patterns locally, obtaining information about the specific clinical diagnoses or procedures for which opioids were prescribed would allow researchers to control for patient characteristics more effectively when assessing variation across prescriber characteristics. Alternatively, researchers may wish to stratify analyses by pain diagnosis or type of procedure to eliminate the effect of diagnosis/procedure on prescribing patterns. They might also design studies to include only one (or similar) pain diagnosis or one (or similar) surgical procedure(s) similar to Eid et al.[39] to describe prescribing patterns and assess for variation. If variation exists, provider characteristics of interest can be assessed as potential drivers of this variation. These approaches would attenuate the potential confounding effect of pain etiology or procedure type on prescribing patterns and improve our understanding of provider-level drivers of variation in opioid prescriptions. Information about specific diagnoses can be obtained by linking the databases used in this thesis to electronic healthcare records or clinical databases that contain more patient-level data. Researchers can also conduct studies to explore physicians' motives for patterns of prescribing using surveys or mixed-methods research designs. It is important

to note however that because excessive opioid prescribing is a multi-factorial problem[40], generating evidence about potential prescribing influencers at various levels (i.e., patient, provider, clinical setting, institute, jurisdiction, etc.) may be necessary for a more comprehensive understanding of determinants of variation.

Researchers can broaden our understanding of opioid prescribing safety using additional approaches. As data continue to be collected in the DIS database, analyzing patterns over time could provide insight about trends and, if policies change over time, the potential influence of such policy-level changes on prescribing patterns. Researchers may also wish to assess variation in prescribing *rates* (i.e., proportion who received a prescriptions versus not) for all patients with a specific pain etiology or surgical procedure, similar to Daoust et al.[34] This would allow researchers to determine what proportion of those with a given diagnosis were prescribed an opioid, and what factors predicted the decision to prescribe or not. Collecting information about high-risk opioid prescribing related to co-prescribing other medications such as benzodiazepines can also be explored to assess prescribing safety. This information is readily available in the DIS database and would be a simple addition to the current dataset analyzed.

6.6 Conclusions

In conclusion, the results of the studies making up this thesis collectively advance our understanding about the safety of opioid prescribing to opioid-naive patients presenting with acute pain or to the acute care setting, and present evidence that is relevant to physicians, patients, medical specialty groups, policymakers, and public health professionals. While I focused on factors that can be evaluated or modified during the clinical encounter – namely, patient demographic and clinical characteristics, and

characteristics of the first written prescription – it is important to recognize that determinants of opioid prescribing patterns and opioid-related harms are multifactorial and multilayered in acute care settings.[40]

A comprehensive assessment of all available evidence, consideration of other important benefits and harms, particularly those that are important to patients, and consideration of patients' values and preferences is paramount for respectful, patient-centred care.[21,41] Therefore, I encourage those who may perceive the evidence in this thesis to be useful for clinical or policy decision-making, to allow it to inform, rather than completely direct, their decisions. I also encourage researchers to use and be critical of the current work, and to be able, through their own future research, to advance our understanding of these issues even further by overcoming current limitations. My hope is that this work will contribute to continuing the forward movement of the field towards achieving the most effective and humane care for all patients involved, while minimizing harms and unintended consequences.

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