PATTERNS OF OPIOID EXPOSURE IN THE EMERGENCY CARE SYSTEM AND PROLONGED OPIOID USE AMONG OPIOID-NAÏVE ADULTS WITH LOW BACK PAIN

by

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DEDICATION

For anyone who has succumbed or lost a loved one to opioids,
and especially for those who were introduced to opioids in the emergency care system.

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ABSTRACT

The objectives of this thesis were to: 1) describe the characteristics of opioids delivered to opioid-naïve adults with low back pain as they transition through a Canadian emergency care system; 2) identify different patterns of opioid exposure; and 3) investigate associations of these patterns with prolonged opioid use. I conducted a retrospective cohort study using linked administrative data in Halifax, Nova Scotia, Canada. I captured opioid delivery at four key points of emergency care management: ambulance, emergency department, discharge, and community pharmacy. I used generalized estimating equations to estimate associations between patterns of opioid exposure and prolonged opioid use, defined as filling an opioid prescription 4-180 days after the index emergency department visit. Opioid-naïve adults with low back pain had varying patterns of opioid exposure in the emergency care system. Patients who received opioids at multiple points in the care process were more likely to transition to prolonged opioid use.

LIST OF ABBREVIATIONS USED

aRR	Adjusted relative risk
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIMD-A	Canadian Index of Multiple Deprivation: Atlantic region
CTAS	Canadian Triage and Acuity Scale
DIS	Drug Information System
ED	Emergency department
EDIS	Emergency Department Information System
EHS	Emergency Health Services
ICD	International Classification of Diseases
IQR	Interquartile range
MASTER-POSTAL	Insured Patient Registry-POSTAL data set
MME	Morphine milligram equivalents
NR	Not reportable
NRS	Numeric rating scale
NS DHW	Nova Scotia Department of Health and Wellness
PMP	Prescription Monitoring Program
Pyxis	BD Pyxis™ MedStation™ ES automated medication dispensing system
QEII ED	Charles V. Keating Emergency and Trauma Centre
REB	Research Ethics Board
RECORD	REporting of studies Conducted using Observational Routinely-collected health Data
RR	Relative risk
Rx	Prescription

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CHAPTER 1 – INTRODUCTION

Canada is in the midst of an opioid epidemic. Since 2016, more than 29,000 Canadians have died of apparent opioid toxicity deaths.[1] These deaths are punctuated by the misuse and diversion of licit opioids, which are often administered and prescribed to manage painful health conditions. In 2018, 13% of Canadians reported using prescription opioids in the past year, of whom 10% engaged in some form of problematic use.[2] In addition, among accidental apparent opioid toxicity deaths occurring in Canada in 2020, 20% involved opioids with pharmaceutical origins.[1] Importantly, 87% of accidental apparent opioid toxicity deaths in Nova Scotia in 2020 involved prescription opioids.[1] Evidently, pharmaceutical opioids play a dominating role in opioid-related harms in Nova Scotia. It is necessary to investigate upstream mechanisms of obtaining opioids in health care that could be contributing to the ongoing public health crisis.

Low back pain is the ideal health condition to explore opioid delivery in the healthcare setting. Low back pain has a unique clinical course in that many individuals who experience an acute episode will go on to develop recurrent or chronic symptoms,[3,4] meaning this patient population faces numerous potential opportunities for opioid prescription. Accordingly, back pain has been identified as one of the most common reasons for which patients receive new opioid prescriptions.[5] Low back pain is also the leading cause of disability in Canada,[6] and four in five Canadian adults will have an episode of low back pain during their lifetime.[7] The emergency department is a common treatment setting for low back pain. Over 150,000 emergency department visits in Canada between 2020-2021 were attributed to a primary complaint of back pain, representing the third most common reason for presentation in the country.[8]

The treatment of low back pain with opioids could represent a gateway to prolonged opioid use and related harms. Prolonged opioid use has been linked to outcomes of misuse (e.g., dependence, overdose), other adverse health effects (e.g., fractures, endocrinologic harms), as well as higher healthcare costs and utilization.[9–11] A 2020 systematic review estimated that up to 61% of adults presenting to the emergency department with low back pain receive opioids during their visit or an opioid prescription at discharge.[12] Emergency department opioid prescribing has been shown to be associated with prolonged opioid use.[13–15] To date, only one study has explored the role of emergency department opioid administration in the context of future opioid use; opioid administration alone (or in combination with opioid prescription) was associated with ongoing opioid use at six months among opioid-naïve patients treated for back pain in the emergency department.[15]

Despite evidence that emergency department opioid administration and prescribing can lead to prolonged opioid use, there remain considerable gaps in our understanding. There is currently insufficient knowledge about what types of opioids are being delivered in emergency care settings, in what quantities, and the routes of administration. Another important gap is the lack of existing evidence describing the different ways or combinations in which people can receive opioids across multiple stages of emergency care management, and whether these differences are important for developing prolonged opioid use. Data from Canadian emergency care settings are also severely lacking, and no studies in Canada have explored the association between opioid administration within the emergency care setting and prolonged opioid use. This study will address these evidence gaps to understand the totality of opioid exposure in the

emergency care system and to explore potential pathways of subsequent prolonged use within the low back pain population.

The objectives of this thesis were to: 1) describe the characteristics of opioids delivered to opioid-naïve adults with low back pain as they transition through a Canadian emergency care system (ambulance, emergency department, discharge, community pharmacy post-emergency department visit); 2) identify patterns of opioid exposure for low back pain in the emergency care system; and 3) investigate associations of these patterns with prolonged opioid use.

This thesis document is comprised of four distinct chapters:

- Chapter 1 introduces the thesis topic and rationale, as well as summarizes the main objectives.
- Chapter 2 provides background information pertaining to the major topic areas of this research, including opioids, low back pain, the emergency care system and community pharmacies in Nova Scotia, guideline recommendations in related areas, and prolonged opioid use.
- Chapter 3 contains a standalone manuscript of a retrospective cohort study examining patterns of opioid exposure for low back pain in the emergency care system and risk of prolonged opioid use.
- Chapter 4 concludes by summarizing the study findings; presenting key strengths, challenges, and limitations of the study; and discussing potential implications for clinical and policy decision-making, directions for future research, and overall significance.

CHAPTER 2 – LITERATURE REVIEW

2.1 Opioids

2.1.1 The Opioid Crisis

Canada is in the midst of an unprecedented opioid crisis. Between January 2016 and December 2021, more than 29,000 Canadians died of apparent opioid toxicity deaths.[1] Of these deaths, 94% were accidental in nature.[1] These fatalities were accompanied by over 30,000 opioid-related poisoning hospitalizations.[1] The rates of opioid-related deaths and hospitalizations have also risen substantially. The average number of opioid toxicity deaths increased from 8 to 21 per day between 2016 and 2021, and opioid-related hospitalizations increased from 14 per day in 2017 to 17 per day in 2021.[1] In Ontario, the annual rate of opioid-related deaths increased by 285% from 1991 to 2015, rising to 53 deaths per million people.[16] Between 2007 and 2017, the annual rate of hospitalizations due to opioid poisoning increased by 53%, to 15.6 hospitalizations per 100,000 people.[17] However, despite national surveillance efforts to monitor opioid-related harms across Canada, the true extent of opioid-related harms remains unknown and is likely underreported.

The magnitude of opioid-related harms in Canada follows a decades-long increase in the production and use of prescription opioids. Since the early 1980s, the quantity of opioids distributed to hospitals and pharmacies for prescriptions in Canada has increased by more than 3,000%.[18] In 2017, more than 21 million prescriptions for opioids were dispensed in Canada.[19] In a 2018 analysis of four Canadian provinces by the Canadian Institute for Health Information, a reported 12.3% of the study population was prescribed opioids.[20] These findings parallel those of the 2018 Canadian Community Health Survey,

which found that 12.7% of Canadians aged 15 years and older used prescription opioids in the past year.[2] The proportion of individuals who reported opioid medication use in the past year was highest in Nova Scotia (15%).[2] As of 2020, Canadians are the eighth highest per capita consumers of opioids in the world.[21]

Prescription opioids are not always used for their intended purposes. For instance, nonmedical prescription opioid use can involve the misuse of prescription opioids by their intended recipient. Among the estimated 3.7 million past-year users of prescription opioids in Canada in 2018, 9.6% engaged in problematic use of these medications (e.g., wanting to get high, tampering with the product).[2] For Canadians who indicated that some or all of their opioids from the past year were prescribed for them, 7% reported that they did not take the medication as directed (e.g., by taking more pills, by medicating more frequently).[2]

Prescription opioids may also be diverted to the substantial detriment of individuals and families. The diversion of licit opioids can occur through many channels; however, many people who misuse prescription opioids obtain them informally from family members or friends. For instance, 47.2% of Americans who misused opioids in 2020 reported obtaining the opioids for their most recent misuse from a family member or friend.[22] Other sourcing pathways for prescription opioids in North America include doctor shopping behaviours, Internet purchases, prescription forgeries or fraud, street drug markets, and theft.[23] These illicit behaviours may have lasting harms on the population; 20% of accidental apparent opioid toxicity deaths in eight Canadian provinces in 2020 involved opioids with pharmaceutical origins.[1] The plethora of diversion routes for prescription opioids and the established dangers of nonmedical

prescription opioid use reinforce the need to investigate upstream opportunities for obtaining opioids in health care that may be contributing to the ongoing public health epidemic.

As a result of widespread opioid prescribing, harms from prescription opioid use predominated in the early stages of the opioid crisis.[18] In recent years, Canada's opioid crisis has primarily been driven by the unregulated drug supply.[18] Of accidental apparent opioid toxicity deaths reported nationwide in 2020, 74% only involved opioids with a non-pharmaceutical origin (i.e., not manufactured by a pharmaceutical company or not approved for medical purposes in humans) and 95% involved fentanyl or fentanyl analogues.[1] Still, prescription opioids play an important role in the ongoing epidemic. Among accidental apparent opioid toxicity deaths occurring in Nova Scotia in 2020, 87% involved opioids with pharmaceutical origins.[1] A better understanding of how opioids are delivered in Nova Scotia's healthcare system may provide insight into what specific, tailored approaches are required to mitigate opioid-related harms in the province.

2.1.2 Types of Opioids

Opioids are a diverse class of drugs with strong analgesic properties. Opioids can be classified according to their synthetic processes, receptors, and pharmacological effects.[24] Natural opioids or 'opiates' (e.g., codeine, morphine) are sourced directly from the opium found in the opium poppy (*Papaver somniferum*), semi-synthetic opioids (e.g., buprenorphine, oxycodone) are partial chemical derivatives of these natural substances, while synthetic opioids (e.g., fentanyl, tapentadol) are entirely manmade but mimic the effects of natural opioids.[24] Opioids exert their pharmacological actions across four main classes of opioid receptors: the classical mu, kappa, and delta receptors, and the

nonclassical nociceptin receptor.[24] Activation of these opioid receptors results in a multitude of effects, including but not limited to analgesia (all receptor types), euphoria (mu), respiratory depression (mu and delta), and dysphoria (kappa).[25,26] At each of the receptors, opioids can act as agonists, partial agonists, or antagonists, which represent measures of efficacy or intrinsic activity.[24] Agonists bind tightly to a receptor to elicit a maximal physiological response, partial agonists bind to a receptor but produce an incomplete functional response, while antagonists do not produce a functional response upon binding with a receptor but prevent agonists from binding to that receptor and exerting their effects.[24] Several opioids, termed 'mixed agonist-antagonists', have dual properties and produce different pharmacological effects at different doses and receptors.[27]

2.1.3 Opioids for Pain Conditions

Opioids are a mainstay of treatment for acute and chronic painful health conditions. In addition to being effective analgesics,[28,29] opioids are an attractive option for acute (including postoperative) pain management due to their availability in many forms for medical use, such as capsules, injectables, liquids, suppositories, tablets, and transdermal patches. Opioids are often more broadly categorized as either 'oral' or 'parenteral' (e.g., intravenous, intramuscular) in the context of acute pain.[30] However, the use of opioids for chronic non-cancer pain is less widely accepted and remains controversial due to concerns about long-term efficacy and potential harms.[31] A 2018 meta-analysis of 96 randomized clinical trials and 26,169 patients with chronic noncancer pain showed that opioids were associated with small improvements in pain and physical functioning, and increased risk of vomiting, compared with placebo, but had similar

benefits for pain and functioning compared to nonopioid alternatives.[32] Still, codeine, fentanyl, and morphine are listed as essential medicines for pain and palliative care by the World Health Organization.[33] Furthermore, a population-based cohort study in Ontario found that the most common condition for which people were initiated on opioids between 2008-2012 in the emergency department or primary care setting was low back pain.[5]

2.2 Low Back Pain

2.2.1 Epidemiology of Low Back Pain

Low back pain is a highly prevalent musculoskeletal disorder and the leading contributor to the global burden of disability.[34] In 2017, low back pain accounted for nearly 65 million years lived with disability, representing an increase of 53% from 1990, and affected more than 575 million individuals worldwide.[34] Increases in disability have been especially marked in countries that have a low Socio-demographic Index (a composite indicator of income per capita, educational attainment, and fertility rate), as they often lack the appropriate health and social resources required to manage the rising burden.[35] The prevalence of low back pain remains highest in countries ranking high on the Index.[35]

Chronic back disorders are prevalent in the Canadian population. A repeated analysis of Canadian Community Health Survey data observed that the prevalence of chronic back disorders was 18.9% in 2007 and 17.8% in 2014.[36] The prevalence was highest among women, in rural areas, and among respondents from Nova Scotia relative to the other provinces and territories.[36] In a nationally-representative survey administered between 2007 and 2008, 22% of adults with chronic pain reported the lower back as the

primary anatomical site of pain and 36% reported any low back pain.[37] In Canada alone, low back pain is experienced by over 5.5 million people at any given time.[6] A population-based survey conducted in two provinces found that four in five adults had experienced at least one episode of low back pain during their lifetime, while one in three adults had experienced one in the previous week.[7] The economic impact of this burden is substantial. Medical expenditures for low back pain in Canada are estimated to be in excess of six billion dollars annually, excluding disability payments and costs related to absenteeism in the workplace.[38] Effective and cost-efficient management of low back pain is urgently needed.

2.2.2 Clinical Course of Low Back Pain

Low back pain is a highly heterogeneous condition with a variable clinical course. It is often defined as pain, muscle tension, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without leg pain.[39] Non-specific low back pain comprises the majority of cases and is a diagnosis of exclusion, meaning that no clear pathoanatomical cause can be identified.[39] Specific causes of low back pain include, but are not limited to, congenital disorders, degenerative conditions, fractures, infections, and tumours.[39,40] Low back pain is considered acute when symptoms persist for less than six weeks, subacute between six weeks and three months, and chronic when symptoms last for longer than three months.[39] Acute episodes of non-specific low back pain have a favourable prognosis, with most symptoms resolving within a couple of weeks.[39] However, a considerable proportion of individuals who experience a low back pain episode will still go on to experience chronic or recurrent symptoms.[41,42] According to

two systematic reviews, about two thirds of patients still report pain one year after onset of the initial episode.[3,4]

2.2.3 Prevalence of Low Back Pain in the Emergency Care System

Low back pain is a common reason for presentation to the emergency care system. A systematic review of 21 publications from 12 countries investigated the prevalence of low back pain in emergency settings, defined as all prehospital, emergency, ambulatory, outpatient, accident, trauma, triage, and urgent care services. The prevalence of low back pain ranged from 0.9% to 17.1% across studies, with a pooled prevalence of 4.4% in standard emergency settings (e.g., emergency departments).[43] This estimate is comparable to emergency department presentations for 'shortness of breath' and 'fever and chills' and would classify low back pain as a top ten presenting complaint in the average American emergency department.[43,44] In 2020-2021, the Canadian Institute for Health Information compiled the most common reasons for emergency department visits across Canada.[8] A total of 150,788 visits were attributed to a chief complaint of back pain across 325 facilities (estimated national coverage of 51%), representing the third most common emergency department presentation in the country.[8] Therefore, low back pain presentations to the emergency care system constitute a considerable portion of healthcare utilization and should not be overlooked.

2.3 The Emergency Care System in Nova Scotia

2.3.1 Prehospital Settings

Emergency medical services refers to the system that oversees all aspects of medical care, planned or unplanned, provided to patients in prehospital settings.[45] Emergency Health Services (EHS), a branch of the Nova Scotia Department of Health

and Wellness, is responsible for delivering emergency medical services in Nova Scotia and for transport to and between hospitals in the province.[46] As of 2021, there are more than 1,000 licensed paramedics in Nova Scotia.[46] They responded to 182,000 calls in 2021.[47] According to a study of non-urgent low back pain presentations at a Nova Scotian emergency department between 2009 and 2015, about 20% of patients arrive by ambulance.[48]

2.3.2 Emergency Department

Emergency medicine is concerned with the assessment, diagnosis, management, and disposition of patients with injury, illness, and behavioural disorders that require rapid care.[49] These conditions are often undifferentiated and include, but are not limited to, acute, life-threatening, and urgent presentations.[49] This care is typically delivered within-hospital; however, the scope of emergency medicine extends beyond the emergency department setting.[49]

Nova Scotia's healthcare system includes 38 emergency departments, including two tertiary care hospitals, nine regional hospitals, 19 community hospitals with emergency departments, and eight collaborative emergency centres.[50] All tertiary care and regional hospitals are required to maintain a 24/7, year-round schedule.[50] The Charles V. Keating Emergency and Trauma Centre (QEII ED), located at one of two tertiary care hospitals in Nova Scotia, is the largest emergency department in Atlantic Canada.[51] The QEII ED receives more than 65,000 patients each year (including approximately 1,500 visits for low back pain),[51] with approximately 30 ambulance arrivals and between 1-6 helicopter arrivals each day.[52]

2.4 Community Pharmacies in Nova Scotia

Community pharmacies (i.e., non-hospital or non-institutional pharmacies) provide neighbourhood-based retail pharmacy services to the public. According to the National Association of Pharmacy Regulatory Authorities, Nova Scotia has a total of 315 accredited community pharmacies as of January 1, 2022.[53] These pharmacies account for the majority of pharmacy establishments and prescription dispensing services in Nova Scotia and dispense roughly 1.8 million prescriptions for monitored drugs, including opioids, each year.[54]

In Nova Scotia, community pharmacies are fully integrated with electronic drug monitoring systems such as the Nova Scotia Prescription Monitoring Program (PMP). The PMP's administrative body, Medavie Blue Cross, receives real-time dispensing and prescription information via an online centralized database.[55] The PMP has a legislated mandate to "promote the appropriate use of monitored drugs in Nova Scotia and to reduce the abuse or misuse of monitored drugs in the province".[56] The PMP monitors drugs listed in Canada's *Controlled Drugs and Substances Act*; most opioids are listed as Schedule I drugs and carry the maximum penalties for offences involving those substances.[56] Importantly, in its 2017-2020 Strategic Plan, the Nova Scotia PMP prioritized improvement of the first opioid prescription (i.e., initiation of opioid therapy).[57]

The scope of electronic prescription monitoring in Nova Scotia has since evolved to include all types of prescription drugs. A province-wide Drug Information System (DIS), established in 2011, allows authorized healthcare providers to access, manage, and share patient medical information to curb prescription drug diversion and to more readily

detect adverse reactions, allergies, or contraindications to specific drugs.[58] Community pharmacies began linking to the DIS in the fall of 2013, and all pharmacies were expected to be connected to the DIS by June 30, 2016.[59] Subsequent phases of implementation have focused on incorporating hospitals and community prescribers, integrating the DIS with Electronic Medical Record systems in clinics and physician offices, and introducing electronic prescribing.[59] The Nova Scotia DIS and PMP now share information in real-time to more effectively support the PMP's mandate.[60]

2.5 Guideline Recommendations

To better situate this study within the current state of opioid prescribing, low back pain management, and pain management in emergency care, I highlight key elements of relevant clinical practice guidelines.

2.5.1 Opioid Prescribing Guidelines

Guidance about opioid prescribing for acute pain (including low back pain) is quite limited. In 2016, the United States Centers for Disease Control and Prevention (CDC) released a comprehensive guideline about opioid prescribing for chronic noncancer pain.[11] This guideline constitutes the most widely cited and endorsed set of recommendations to date, with the primary intent to inform primary care clinicians who encounter adult chronic pain patients (excluding those in active cancer treatment, palliative care, and end-of-life care) in outpatient settings.[11] The CDC guideline also briefly addresses nonsurgical, nontraumatic acute pain conditions, stating that opioids should only be prescribed in this context when warranted (based on diagnosis or severity of pain) and only in the lowest effective dose of immediate-release opioids.[11] The guideline also suggests that opioid prescriptions of three days or less are typically

sufficient for acute pain control and that prescriptions exceeding seven days will rarely be needed.[11]

In 2018, a systematic review summarized recommendations from four clinical practice guidelines about safe opioid prescribing practices for acute, noncancer pain in hospital settings.[61] The guidelines were produced by the American College of Emergency Physicians, the National Institute for Health and Care Excellence, the American College of Occupational and Environmental Medicine, and the Washington State Agency Medical Directors' Group.[61] All four guidelines recommended prescribing a limited duration of opioids over the entire acute pain episode (approximately 1-2 weeks of opioids at most).[61] Most guidelines recommended restricting opioids to severe pain or pain that has not resolved with nonopioid therapy, using the lowest effective dose of immediate-release opioids, and checking prescription drug monitoring programs when prescribing.[61] Other overlapping recommendations across guidelines included: co-prescribing with nonopioid analgesics, setting goals and expectations for patient recovery, educating patients about risks and informing them about proper safekeeping and safe disposal practices, using opioids as needed and not at scheduled doses, using an opioid dose conversion guide when prescribing, and avoiding co-administration of parenteral and oral opioids.[61]

2.5.2 Low Back Pain Guidelines

There are numerous guidelines that provide generally consistent recommendations regarding the diagnosis and treatment of non-specific low back pain. Among these guidelines are the 2016 guideline from the National Institute for Health and Care Excellence and the 2017 guideline from the American College of Physicians, both of which have been widely cited and endorsed by physician organizations.[62,63] A 2018

systematic review by Oliveira and colleagues summarized recommendations about non-specific low back pain from 15 international clinical practice guidelines published between 2008 and 2017, representing the most comprehensive review to date.[64] For the diagnosis of low back pain, the guidelines consistently recommended diagnostic triage, history taking, and physical examination to identify red flags (e.g., fracture, infection, malignancy); neurological testing to identify radiculopathy; no routine imagine unless serious pathology is expected; and assessment of psychosocial factors (e.g., patient beliefs, social support, treatment preferences).[64]

Treatment recommendations for low back pain were based on the duration of symptoms. For acute low back pain, the guidelines endorsed patient education, advice on resuming normal activities, avoiding bed rest, reassurance about a favourable prognosis, and the use of nonsteroidal anti-inflammatory drugs (or weak opioids for short periods when nonsteroidal anti-inflammatory drugs are contraindicated or do not improve symptoms).[64] For chronic low back pain, the guidelines recommended the use of nonsteroidal anti-inflammatory drugs and antidepressants as needed, exercise therapy, psychosocial interventions, and referral to a specialist when serious pathology or radiculopathy is suspected.[64]

2.5.3 Emergency Care Guidelines

In contrast to guidelines for opioid prescribing and low back pain management, a standard, widely adopted guideline for prehospital adult pain management does not exist. The existing evidence on prehospital pain management was summarized in a 2019 systematic review, though the review authors cited insufficient evidence and a lack of detail as limitations.[65] A total of 12 guidelines and protocols were included in the review,

all of which endorsed the use of a standard method of pain assessment (e.g., the Numeric Rating Scale or the Visual Analogue Scale) in the prehospital environment.[65] For patients with mild pain, most guidelines recommended acetaminophen as the medication of choice, with a reduced dose for patients who are older, malnourished, or who weigh less than 60 kilograms.[65] For patients with moderate or severe pain, most guidelines recommended first-line treatment with morphine or fentanyl.[65] Several guidelines also endorsed the use of ketamine for patients experiencing severe pain.[65] Overall, there was little agreement between guidelines regarding correct dosages for medication administration. Nevertheless, the results of the review suggest that opioid delivery is an important component of prehospital pain management for adults.

In 2018, the American Academy of Emergency Medicine endorsed guidelines for the safe and effective treatment of acute pain in the emergency department.[30] Key recommendations for emergency physicians include communicating with patients about the goals of emergency department pain management (restoration of functional ability, not just reducing pain), engaging patients in shared decision-making, expressing an understanding of the patient's suffering, weighing the potential benefits and harms of analgesic options, and utilizing combinations of nonpharmacological and pharmacological therapies.[30] In line with the American College of Emergency Physicians' recommendations for opioid prescribing,[66] these guidelines strongly recommend the use of nonopioid and nonpharmacologic modalities to treat acute pain in the emergency department whenever possible, and to only consider opioids when the benefits outweigh the harms.[30] More specifically, the guidelines state that morphine should be the oral opioid of choice as levels of euphoria are lower compared to other

opioids, parenteral opioids should only be used with caution at low doses (titrated upwards as needed), opioid prescriptions should be limited to 2-3 days of an immediate-release formulation, and patients should be advised on the risks of opioid dependence and tolerance.[30]

2.6 Opioids, Low Back Pain, and the Emergency Care System

Although guidelines caution against the use of opioids for the treatment of low back pain in emergency care, opioids are frequently administered and prescribed within this context. In a population-based cohort study of 34,713 adults who were initiated on an opioid by an emergency physician, back pain was the most common diagnosis.[5] In fact, a 2020 systematic review by Kamper and colleagues estimated that up to 61% of patients presenting to the emergency department with low back pain receive opioids either during their visit or at discharge.[12] One of the included studies, based at the QEII ED, found that 34.5% of adults who presented to the emergency department with non-urgent low back pain received an opioid during their stay and 38.5% received an opioid prescription at discharge.[48] The treatment of low back pain with opioids could represent a gateway to prolonged opioid use and related harms; the recurrent nature of low back pain provides numerous potential opportunities for opioid prescription. Low back pain is therefore the ideal condition to explore potential mechanisms of prolonged opioid use that originate in the emergency care setting.

2.7 Prolonged Opioid Use

2.7.1 Prolonged Opioid Use Definitions

Prolonged opioid use, a general term that encompasses opioid use beyond a first opioid prescription or opioid initiation period, is inconsistently defined in the literature.

Most prolonged opioid use definitions capture one of the following constructs: 1) one additional opioid prescription fill within a specified time interval; 2) multiple additional opioid prescription fills within a specified time interval; 3) the days' supply within a specified time interval; 4) the duration of opioid use; or 5) a composite measure of different criteria. However, there is a lack of harmonization across studies in terms of how these constructs are measured and labeled. More commonly used labels include additional use, continued/continuous use, episodic use, long-term use, persistent use, and recurrent use, but the usefulness of this terminology is limited. In Table 2.1, I provide a summary of various definitions of prolonged opioid use used in the literature.

Table 2.1. Operationalization and prevalence of prolonged opioid use in the literature.

	Operationalization of prolonged opioid use				
Study	**Label**	**Definition**	**Time interval**	**Setting**	**Prevalence (%)***
Construct: One additional prescription fill					
Thiels 2019[67]	Additional	1 fill	90-180 days after surgery	Population-level	7.89-10.41
Alam 2012[68]	Long-term	1 fill	±60 days of 1 year after surgery	Population-level	10.3
Brummett 2017[69]	Persistent	1 fill	90-180 days after surgery	Population-level	5.9-6.5
Olds 2019[70]	Persistent	1 fill	90-180 days after surgery	Population-level	10.0
Hoppe 2015[13]	Recurrent	1 fill	±60 days of 1 year after index visit	Emergency department	17
Schroeder 2019[71]	-	1 fill	90-365 days after index fill or phantom date	Population-level	6.9
Construct: Multiple additional prescription fills					
Webster 2007[72]	Continued/Late	≥5 fills	30-730 days post-onset of pain	Population-level	-
Deyo 2017[73]	Long-term	≥6 fills	Within 1 year after initiation month	Population-level	5.0
Azad 2019[74]	Long-term	≥6 fills	Within 1 year after index visit	Population-level	-

	Operationalization of prolonged opioid use				
Study	**Label**	**Definition**	**Time interval**	**Setting**	**Prevalence (%)***
Lee 2016[14]	Long-term	≥3 fills	4 days-12 months post-onset of injury	Emergency department	-
Friedman 2020[75]	Persistent	≥6 fills	Within 6 months after index visit	Emergency department	1
Olds 2019[70]	Prolonged	1 fill + 1 fill	90-180 days after surgery and 181-365 days after surgery	Population-level	3.5
Hayden 2021[76]	Prolonged	1 fill + 1 fill	8-90 days after index visit and 150-210 days after index visit (with no more than 180 days between fills)	Emergency department	4.6
Friedman 2020[75]	Recurrent	≥2 fills	Within 6 months after index visit	Emergency department	21
Construct: Days' supply					
Dobscha 2013[77]	Chronic opioid therapy/Long-term	≥90 consecutive days' supply	Within 1 year after index visit	Veterans Affairs facilities	-
Barnett 2017[78]	Long-term	≥180 days' supply	Within 1 year after index visit	Emergency department	-
Zin 2019[79]	Long-term	≥90 days' supply	Within 1 year after index fill	Tertiary hospitals	11.64
Construct: Duration of opioid use					
Shah 2017[80]	Continued	Did not meet definition for discontinuation†	Within 1 year after index fill	Population-level	5.3
Thiels 2019[67]	Persistent	Episode lasting ≥90 days	Starting in the 180 days after surgery	Population-level	1.07-4.29
Construct: Composite measure					
Hooten 2015[81]	Chronic	Episode lasting ≥90 days with either ≥10 fills or ≥120 days' supply	Within 1 year after index fill	Population-level	6
Thiels 2019[67]	CONsortium to Study Opioid Risks and Trends	Episode lasting ≥90 days with either ≥10 fills or ≥120 days' supply	Starting in the 180 days after surgery	Population-level	0.47-2.31

	Operationalization of prolonged opioid use				
Study	**Label**	**Definition**	**Time interval**	**Setting**	**Prevalence (%)***
Hooten 2015[81]	Episodic	Episode lasting >90 days with <10 fills and <120 days' supply	Within 1 year after index fill	Population-level	21
Fritz 2018[82]	Long-term	≥120 days' supply or episode lasting >90 days with ≥10 fills	Within 1 year after index visit	Population-level	24.3
Jeffery 2018[83]	Long-term	Episode lasting ≥90 days with either ≥10 fills or ≥120 days' supply	Within 1 year after index fill	Population-level	1.8-13.4

* Prevalence estimates are only included for studies that measured prolonged opioid use among opioid-naïve patients following a first opioid prescription or an opioid initiation period.
† Opioid discontinuation was defined as at least 180 continuous days without opioid use from the end date of the last opioid prescription.

Existing definitions of prolonged opioid use are not without limitations. For instance, in studies that operationalize prolonged opioid use as an additional prescription around one year after an index visit, the additional prescription could be filled for an entirely independent clinical problem than the initial visit. A similar issue arises when prolonged opioid use is defined as multiple additional prescription fills within a defined interval, because physicians are increasingly being encouraged to prescribe shorter prescriptions.[61] Therefore, it would be reasonable to expect that patients could fill multiple prescriptions over a short period of time to resolve an episode of acute pain. If these prescriptions are filled many months after an initial visit, the opioids could be prescribed for an independent clinical problem. If these prescriptions are filled in quick succession after an initial visit, the prescriptions may no longer be a good measure of prolonged use. Finally, when prolonged opioid use is defined in terms of the days'

supply, there is a risk of overestimating actual opioid use if individuals are not consuming the entire dose as prescribed.

2.7.2 Potential Harms

Prolonged opioid use is associated with many negative outcomes. In the 2016 CDC guideline about opioid prescribing for chronic noncancer pain, the authors identified several potential harms, including a dose-dependent increased risk of fatal and nonfatal overdose, an increased risk of receiving an opioid abuse or dependence diagnosis, and increased risks of adverse health effects such as fractures, myocardial infarction, and endocrinologic harms.[11] However, the overall strength of evidence was low.[11] In a qualitative review of potential adverse effects of long-term opioid therapy, Baldini and colleagues summarized harms across several organ systems.[84] Adverse events included constipation, fractures, hypothalamic-pituitary-adrenal dysregulation, negative cardiovascular effects, sleep disturbance, and overdose, with the authors citing a need for additional research in this area.[84] Importantly, prolonged opioid use has been associated with higher healthcare costs and utilization.[9,10]

2.7.3 Prevalence of Prolonged Opioid Use

An emerging body of literature has found evidence of prolonged opioid use among opioid-naïve individuals who receive opioids for an acute condition. This opioid-naïve population is typically defined as individuals who have not filled an opioid prescription over an extended period of time (usually three months[82], six months,[67,74,75,78,80,81,83] or one year[13,69–71,73,77,79,85]), as a proxy for no opioid exposure at baseline. I performed a scoping search of the literature to obtain estimates for the prevalence of prolonged opioid use following a new opioid prescription fill or opioid

initiation period. As expected, the prevalence of prolonged opioid use varied considerably, ranging from 0.47% to 24.3%, due to substantial differences in definitions used (Table 2.1).

2.7.4 Risk Factors for Prolonged Opioid Use

Emergency department opioid prescribing has been shown to be associated with prolonged opioid use. A study by Hoppe et al. found that opioid-naïve patients who filled an emergency department opioid prescription for acute pain were more likely to fill an opioid prescription one year after their emergency department visit than patients who did not receive an opioid prescription.[13] Heard et al. found that opioid-naïve patients discharged from the emergency department with back pain who were given an opioid prescription had increased risk of ongoing opioid use at six months compared to those that did not receive any opioids.[15] This latter study also observed that emergency department opioid administration alone, and the combination of opioid administration and opioid prescription, increased the risk of ongoing opioid use.[15] To date, there are no data from Canada reporting on the association between opioid administration in the emergency department (or more broadly in the emergency care system) and prolonged opioid use.

Various patient, physician, and prescription factors are associated with prolonged opioid use following new use for acute pain. Patient factors related to prolonged opioid use include older age; female sex; lower education; a history of alcohol, drug, or tobacco use; and anxiety and mood disorders.[69,76,81,85] With respect to physician factors, a study of 377,629 opioid-naïve patients who had an emergency department visit between 2008 and 2011 found that patients who were treated by high-intensity prescribers (relative to

quartiles of prescribing rates within the same hospital) were more likely to have long-term opioid use than patients treated by low-intensity prescribers (adjusted odds ratio 1.30; 95% confidence interval [CI]: 1.23-1.37).[78] Prescription characteristics that are associated with prolonged opioid use include higher dose, increasing days' supply, and initiating with tramadol or long-acting (versus short-acting) formulations.[67,72,76,79,80]

2.8 Need for Research

A small number of studies have made significant strides toward understanding how emergency department opioid administration and prescribing relate to prolonged opioid use. However, there is still substantial work to be done to address crucial evidence gaps in the literature:

1. To date, there is insufficient knowledge about characteristics of opioids delivered to opioid-naïve adults in the prehospital and emergency department settings.
2. Studies have largely overlooked the different ways in which people can receive opioids as they transition through the emergency care system (i.e., whether there are different patterns of opioid exposure that exist).
3. There is a paucity of evidence on the association between patterns of opioid exposure across the emergency care system and prolonged opioid use, and currently no available data from Canada.

Opioids delivered in the prehospital setting, in the emergency department, at discharge, and at the community pharmacy following an emergency department prescription are not independent events. This study will address the above-mentioned knowledge gaps to better understand the complexity and interconnected nature of opioid exposure across the emergency care system, and to explore whether, and to what extent,

opioid exposures originating in the emergency care system increase the risk for subsequent prolonged opioid use within the low back pain population.

CHAPTER 3 – PATTERNS OF OPIOID EXPOSURE FOR LOW BACK PAIN IN THE EMERGENCY CARE SYSTEM AND RISK OF PROLONGED OPIOID USE

3.1 Abstract

Objective: We aimed to: 1) describe the characteristics of opioids delivered to opioid-naïve adults with low back pain as they transition through the emergency care system; 2) identify patterns of opioid exposure for low back pain in the emergency care system; and 3) investigate associations of these patterns with prolonged opioid use.

Methods: We conducted a retrospective cohort study of opioid-naïve adults presenting to a tertiary care emergency department with low back pain between April and September 2020 (Halifax, Nova Scotia, Canada). We used linked administrative data to capture opioid delivery at four key points of emergency care management: ambulance, emergency department, discharge, and community pharmacy. We used generalized estimating equations with log function and Poisson family, clustered by emergency department provider, to estimate associations between patterns of opioid exposure and prolonged opioid use, defined as filling an opioid prescription 4-180 days after the index emergency department visit.

Results: Of 445 patients, 131 (29.4%) received opioids in the emergency care system. Among patients who received opioids, the most common patterns of exposure were discharge only (18.3%), emergency department and discharge (16.0%), and emergency department only (14.5%). In total, 54 individuals (12.1%) met the criteria for prolonged opioid use. Compared to patients who did not receive opioids, patients who received opioids in the ambulance/emergency department, at discharge, and filled an opioid prescription from the emergency department had the highest risk of prolonged opioid use (adjusted relative risk 3.85, 95% confidence interval: 1.87-7.92).

Conclusions: Opioid-naïve adults with low back pain had varying patterns of opioid exposure in the emergency care system. Patients who received opioids at multiple points in the care process were more likely to transition to prolonged opioid use.

3.2 Introduction

3.2.1 Background

Since 2016, more than 29,000 Canadians have died of apparent opioid toxicity deaths.[1] These deaths are punctuated by the misuse and diversion of licit opioids; in 2018, 13% of Canadians reported using prescription opioids in the past year, of whom 10% engaged in some form of problematic use.[2] Low back pain, the leading cause of disability in Canada,[6] is one of the most common reasons for which people are prescribed opioids and a top presenting complaint in the emergency department.[5,43,44] Back pain was responsible for over 150,000 emergency department visits in Canada between 2020-2021 – the third most frequent reason for presentation in the country.[8] Importantly, a 2020 systematic review reported that between 17% and 61% of adults presenting to the emergency department with low back pain receive opioids.[12]

3.2.2 Importance

Prolonged opioid use is an important sequela of opioid delivery for acute pain in the emergency care setting. Prolonged opioid use has been linked to outcomes of misuse, including opioid dependence and overdose; other adverse health effects, including cardiovascular events, endocrinologic harms, and fractures; as well as higher healthcare costs and utilization.[9–11] Prior studies have identified an association between emergency department opioid prescribing and prolonged opioid use,[13,14] and previously reported rates of prolonged use after an initial opioid prescription from the emergency department

range from 1% to 21%.[13,75,76,78,85] More recently, Heard et al. found that emergency department opioid administration alone, opioid prescription alone, and the combination of opioids administered and prescribed were associated with ongoing opioid use at six months among opioid-naïve patients treated for back pain in the emergency department.[15]

To date, existing research has not considered the different ways in which patients can receive opioids across multiple stages of emergency care management (prehospital, emergency department, discharge, prescription), or corresponding associations with prolonged opioid use. There are also no studies in Canada, and only one study from the United States,[15] that have estimated the risk of prolonged opioid use following exposure to opioids within the emergency care system. The magnitude of opioid-related harms in Canada underscores the need to probe opioid delivery across the entire emergency care setting as a potential point of entry to the ongoing public health crisis.

3.2.3 Goals of This Investigation

We aimed to: 1) describe the characteristics of opioids delivered to opioid-naïve adults with low back pain as they transition through a Canadian emergency care system (ambulance, emergency department, discharge, community pharmacy post-emergency department visit); 2) identify patterns of opioid exposure for low back pain in the emergency care system; and 3) investigate associations of these patterns with prolonged opioid use.

3.3 Methods

3.3.1 Study Design and Setting

We conducted a retrospective cohort study based at the Charles V. Keating Emergency and Trauma Centre (QEII ED) in Halifax, Nova Scotia, Canada. We followed

the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement for reporting observational studies using routinely collected health data (Appendix 1).[86] The Nova Scotia Health Research Ethics Board approved the study (REB #1026137).

3.3.2 Selection of Participants

We included opioid-naïve adults who presented to the QEII ED with low back pain between April 9, 2020, and September 30, 2020 (Figure 3.1). We defined opioid-naïve as no opioid prescription fill in the six months preceding the emergency department visit. We defined low back pain as presenting to the emergency department with a chief complaint of 'back pain' or 'traumatic back/spine injury' and receiving a relevant non-specific or mechanical/radicular low back pain discharge diagnosis using International Classification of Diseases (ICD) 9/10 codes (Appendix 2). If an individual had more than one eligible emergency department visit during the period of interest, we selected the first presentation as the index visit. We excluded individuals who were under 18 years of age, did not have a valid Nova Scotia Health Card Number, had a planned emergency department visit, went directly to consult, left against medical advice, were admitted to the hospital, or required surgery. All patients had complete prescription data available six months before and six months after their index emergency department visit to ensure complete capture of the opioid-naïve eligibility period and complete data for outcome measurement. The study population selection process is elaborated in Appendix 3.

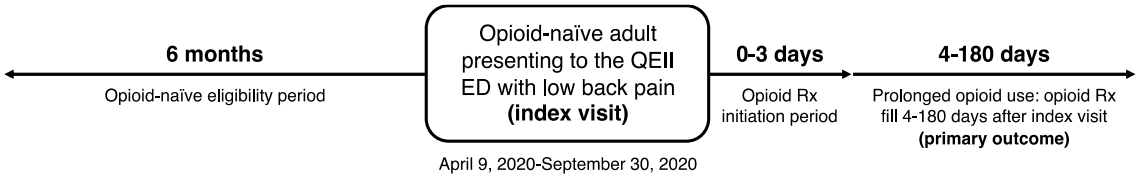

Figure 3.1. Study time frames: opioid-naïve eligibility period, index opioid prescription initiation period, and observation window for prolonged opioid use.

3.3.3 Data Sources

We used linked routinely collected person-level data from five administrative clinical and drug monitoring databases: the Emergency Health Services (EHS) database, the Emergency Department Information System (EDIS), the BD Pyxis™ MedStation™ ES automated medication dispensing system (Pyxis), the Nova Scotia Drug Information System (DIS), and the Insured Patient Registry-POSTAL (MASTER-POSTAL) data set, as well as the geographically based Canadian Index of Multiple Deprivation: Atlantic region (CIMD-A) data set.[87] EHS contains patient data, operational characteristics, and information on medications (including opioids) delivered in the ambulance setting or offload delay period. EDIS includes clinical and demographic characteristics on all patients presenting to the QEII ED. Pyxis records real-time data about medications (including opioids) as they are dispensed in the emergency department. There are four Pyxis machines located in the QEII ED. DIS includes information for all prescriptions filled at community pharmacies in the province of Nova Scotia. MASTER-POSTAL was used to determine the postal code of each patient at the time of their index QEII ED encounter. Postal code was linked with CIMD-A to provide a proxy measure of individual-level socioeconomic status. The CIMD-A uses microdata from the 2016 Census of Population to measure deprivation within four dimensions (economic

dependency, ethno-cultural composition, residential instability, and situational vulnerability) at the dissemination area-level.[87] Dissemination areas represent the smallest geographical units for which all census data are distributed in Canada and typically encompass 400 to 700 persons.[87]

3.3.4 Measurements

Patient demographic characteristics of interest included age, sex, availability of primary care provider, responsibility for payment (Nova Scotia Department of Health and Wellness, Workers' Compensation Board), and quintiles (for description) or scores (for analysis) of the four CIMD-A dimensions (economic dependency, ethno-cultural composition, residential instability, and situational vulnerability). Patient clinical characteristics included time of presentation (weekday, working hours), method of arrival (ambulance, friend or relative, self), the Canadian Triage and Acuity Scale (CTAS) score (1=resuscitation, 2=emergent, 3=urgent, 4=less urgent, and 5=non-urgent; levels 4 and 5 were combined for analysis), pain intensity score, length of stay in the emergency department, and low back pain discharge diagnosis (non-specific, mechanical/radicular).

Characteristics of opioids delivered in the ambulance or in the emergency department were opioid type, dose, number of administrations, and route of administration (oral, parenteral/other). We reported dose in terms of oral morphine milligram equivalents (MME); MME conversion factors were sourced from two Canadian guidelines and are provided in Appendix 4.[88,89] At discharge from the emergency department, we captured opioid type, dose, route of administration, and number of tablets. We consulted local emergency physicians to assist with decisions differentiating opioids administered in the emergency department (i.e., during the visit)

and opioids distributed at discharge in the Pyxis database.

We also described characteristics of the index opioid prescription. We considered an opioid prescription to be related to the index emergency department visit (i.e., prescribed by the emergency department physician) if it was filled within three days post-discharge. If a patient filled more than one opioid prescription within three days after the emergency department visit, we only considered the first prescription as the index prescription. Relevant characteristics included days between the index visit and index prescription fill, whether a long-acting opioid was received, dose (measured as a continuous variable and categorized as <50 MME/day and ≥50 MME/day for description), and days' supply (measured as a continuous variable and categorized as ≤3 days and >3 days for description). The dose for opioid prescriptions was the average daily MME, calculated by taking the total MME dispensed over the days' supply. The categories for description were based on recommended limits in the Centers for Disease Control and Prevention Guideline for prescribing opioids for chronic pain.[11]

The main exposures of interest were the different patterns of opioid exposure for low back pain in the emergency care system. For description, each patient was categorized into a mutually exclusive group based on whether and where the patient received opioids across four potential points of delivery: in the ambulance (including on patient contact, during transport, and the offload delay period), in the emergency department, at discharge from the emergency department, and a prescription fill at the community pharmacy likely attributed to an emergency department prescription, where each possible exposure pathway was considered a unique category. For analysis, we operationalized our exposure of interest in six ways and explored associations with

prolonged opioid use in separate models: any ambulance opioid exposure, any emergency department opioid exposure, any discharge opioid exposure, any opioid prescription fill, the cumulative number of opioid exposures, and the combinations of opioid exposure. Table 3.1 describes the six exposure variables in detail. We grouped certain patterns of opioid exposure together due to small frequencies for some patterns, while considering the similarity and clinical relevance of such groupings in advance of performing analyses.

Table 3.1. Description of exposure variables.

Pattern/variable[*]	**Categories**
1. Any ambulance opioid exposure	a. Did not receive opioids in the ambulance *(reference group)* b. Received opioids in the ambulance, irrespective of other opioid exposures
2. Any ED opioid exposure	a. Did not receive opioids in the ED *(reference group)* b. Received opioids in the ED, irrespective of other opioid exposures
3. Any discharge opioid exposure	a. Did not receive opioids at discharge *(reference group)* b. Received opioids at discharge, irrespective of other opioid exposures
4. Any opioid prescription fill	a. Did not fill an opioid prescription *(reference group)* b. Filled an opioid prescription, irrespective of other opioid exposures
5. Cumulative number of opioid exposures	a. None *(unexposed; 1° reference group)* b. One *(2° reference group)* c. Two d. Three or four
6. Combinations of opioid exposure[†]	a. None *(unexposed; 1° reference group)* b. Opioids administered in the ambulance and/or ED *(ambulance/ED; 2° reference group)* c. Opioids delivered at discharge and/or a filled opioid prescription *(discharge/prescription)* d. Opioids administered in the ambulance/ED and opioids delivered at discharge *(ambulance/ED + discharge)* e. Opioids administered in the ambulance/ED and a filled opioid prescription *(ambulance/ED + prescription)* f. Opioids administered in the ambulance/ED and opioids delivered at discharge and a filled opioid prescription *(ambulance/ED + discharge + prescription)*

ED, emergency department.
[*] Within each variable, the categories are mutually exclusive.
[†] Similar patterns were grouped together due to small frequencies for some patterns.

3.3.5 Outcomes

Our outcome of interest was prolonged opioid use, defined as filling an opioid prescription 4-180 days after the index emergency department visit. We conducted sensitivity analyses using an alternative definition of prolonged opioid use: filling an opioid prescription 91-180 days after the index emergency department visit.

3.3.6 Analysis

We described patient characteristics and opioid characteristics using frequencies (with proportions) for categorical variables and medians (with interquartile ranges [IQRs]) for continuous variables. We employed a modified directed acyclic graph to identify potential confounding variables, using key concepts to describe hypothesized relationships between patterns of opioid exposure in the emergency care system and prolonged opioid use (Appendix 5) and subsequently mapping each concept to a representative variable in our linked data set (Appendix 6). Age, availability of primary care provider, economic dependency score, ethno-cultural composition score, residential instability score, situational vulnerability score, length of stay, CTAS score, responsibility for payment, and sex were identified as potential confounders.

We reported the prevalence of the different patterns of opioid exposure in the emergency care system and of prolonged opioid use in the overall study sample. To estimate associations between patterns of opioid exposure and prolonged opioid use, we used a generalized estimating equations approach with Poisson family, log link, an exchangeable working correlation structure, and robust standard errors clustered at the level of the emergency department healthcare provider, to take into account the dependence of the data.[90] We conducted a complete case analysis (missing data are

described in Table 3.2) and presented crude and adjusted associations as relative risks (RRs) with 95% confidence intervals (95% CIs). All analyses were conducted using Stata/MP version 15.1 (StataCorp, College Station, TX).

3.4 Results

3.4.1 Characteristics of Study Subjects

There were 459 opioid-naïve adults who presented to the QEII ED with low back pain during the study period. Of these, we excluded 14 individuals for not meeting the eligibility criteria: seven went directly to consult or had a planned visit, five were ineligible based on their disposition (admitted, left against medical advice, required surgery), and two were from out of province. Therefore, 445 patients were available for analyses (Figure 3.2).

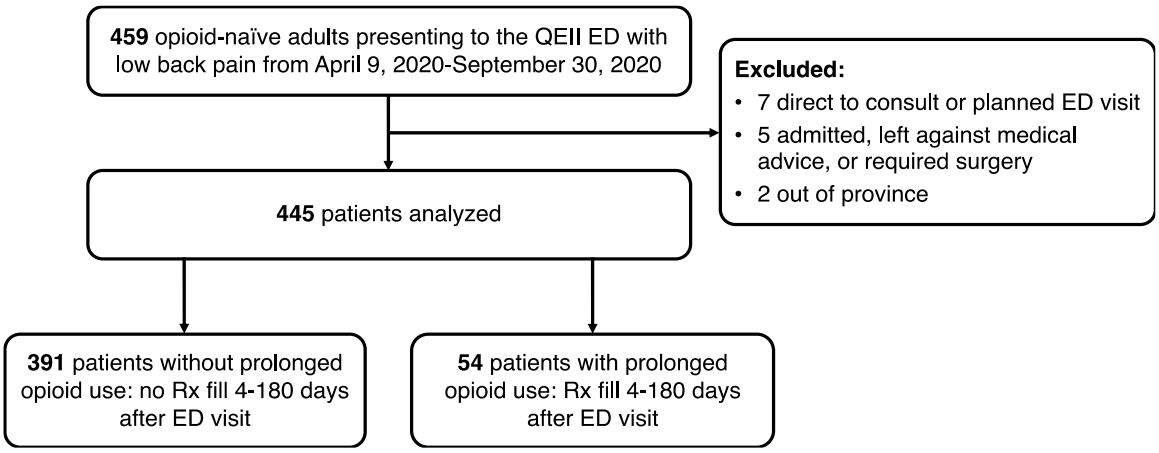

Figure 3.2. Study population.

The median age of participants was 46 years (IQR: 33-60), 49.7% were female, and most individuals (85.8%) had a primary care provider on record. Patients most commonly presented to the emergency department on their own (79.1%); 60 patients (13.5%) arrived by ambulance. Most patients (70.1%) had a CTAS score of 3 (urgent) and the median pain intensity at presentation was 5 on a 0-10 scale (IQR: 2-7). The

median length of stay in the emergency department was 3.3 hours (IQR: 2.2-4.9), with 66.7% of patients receiving a non-specific low back pain diagnosis at discharge and 33.3% receiving a mechanical/radicular low back pain diagnosis. Table 3.2 provides detailed description of the sample.

Table 3.2. Demographic and clinical characteristics of the study sample.

Characteristic	No. (%) of patients* n=445
Demographic	
Age, yr, median (IQR)	46 (33-60) range: 18-94
Female sex	221 (49.7)
Availability of primary care provider	382 (85.8)
Responsibility for payment	
NS DHW	402 (90.3)
Workers' Compensation Board	43 (9.7)
Economic dependency quintile	
Q1 (least deprived)	201 (45.2)
Q2	112 (25.2)
Q3	63 (14.2)
Q4	48 (10.8)
Q5 (most deprived)	19 (4.3)
Missing	2 (0.5)
Ethno-cultural composition quintile	
Q1 (least deprived)	13 (2.9)
Q2	17 (3.8)
Q3	35 (7.9)
Q4	84 (18.9)
Q5 (most deprived)	294 (66.1)
Missing	2 (0.5)
Residential instability quintile	
Q1 (least deprived)	47 (10.6)
Q2	57 (12.8)
Q3	37 (8.3)
Q4	61 (13.7)
Q5 (most deprived)	241 (54.2)
Missing	2 (0.5)
Situational vulnerability quintile	
Q1 (least deprived)	188 (42.3)
Q2	96 (21.6)
Q3	68 (15.3)
Q4	38 (8.5)
Q5 (most deprived)	53 (11.9)
Missing	2 (0.5)

Characteristic	No. (%) of patients* n=445
Clinical	
Time of presentation	
Weekday	313 (70.3)
Working hours (M-F 8AM-5PM)	179 (40.2)
Method of arrival	
Ambulance	60 (13.5)
Friend or relative	33 (7.4)
Self	352 (79.1)
CTAS score	
1 (resuscitation)	0
2 (emergent)	41 (9.2)
3 (urgent)	312 (70.1)
4 (less urgent)	87 (19.6)
5 (non-urgent)	5 (1.1)
Pain intensity, NRS /10, median (IQR)†	5 (2-7) range: 0-10
Length of stay, hr, median (IQR)	3.3 (2.2-4.9) range: 0.6-23.8
Low back pain diagnosis	
Non-specific	297 (66.7)
Mechanical/radicular	148 (33.3)

CTAS, Canadian Triage and Acuity Scale; IQR, interquartile range; NRS, numeric rating scale; NS DHW, Nova Scotia Department of Health and Wellness.
* Percentages may not total 100 because of rounding.
† Missing n=351.

3.4.2 Characteristics of Opioids Delivered in the Ambulance

Of the 60 patients who arrived to the QEII ED by ambulance, 25 (41.7%) received opioids (Table 3.3). Twenty-one patients (84.0%) received fentanyl, while eight patients (32.0%) received morphine. The median dose of opioids delivered in the ambulance was 30 MME (IQR: 30-60) and the median number of opioid administrations was 3 (IQR: 2-4).

3.4.3 Characteristics of Opioids Delivered in the Emergency Department or at Discharge

Of the 445 study participants, 76 (17.1%) received opioids during their emergency department visit (Table 3.3). The most common type of opioid delivered was hydromorphone (50.0%), followed by morphine (29.0%), and codeine (18.4%). The

median dose of opioids delivered in the emergency department was 10 MME (IQR: 9-30) and the median number of opioid administrations was 1 (IQR: 1-1). Most participants (75.0%) received oral opioids.

At discharge, 70 (15.7%) of 445 patients received opioids (Table 3.3). Of these, 41 (58.6%) received hydromorphone, 18 (25.7%) received codeine, and 11 (15.7%) received morphine. The median dose of opioids and the median number of tablets sent home with patients was 27 MME (IQR: 20-40) and 4 tablets (IQR: 2-5), respectively.

Table 3.3. Characteristics of opioids delivered to patients in the ambulance, in the emergency department, and at discharge.

	No. (%) of patients receiving opioids		
Characteristic	**Ambulance*** **n=25**	**Emergency department n=76**	**Discharge n=70**
Opioid type			
Codeine	-	14 (18.4)	18 (25.7)
Fentanyl	21 (84.0)	NR	0
Hydromorphone	0	38 (50.0)	41 (58.6)
Morphine	8 (32.0)	22 (29.0)	11 (15.7)
Total dose received, oral MME, median (IQR)	30 (30-60) range: 30-105	10 (9-30) range: 4.5-60	27 (20-40) range: 5-60
Number of administrations, median (IQR)	3 (2-4) range: 2-10	1 (1-1) range: 1-4	-
Route of administration			
Oral	0	57 (75.0)	70 (100.0)
Parenteral/other	25 (100.0)	19 (25.0)	0
Number of tablets received, median (IQR)	-	-	4 (2-5) range: 1-6

IQR, interquartile range; MME, morphine milligram equivalents; NR, not reportable (cell size less than 5).
- means not applicable.
* Two patients who arrived at the emergency department by ambulance were missing Emergency Health Services data; therefore, we were unable to assess opioid delivery in the ambulance setting. These patients were assumed to not have received opioids in the ambulance and are therefore not represented in this table. Patients who received both morphine and fentanyl were counted in both categories.

3.4.4 Characteristics of the Index Opioid Prescription

Forty-nine (11.0%) patients filled an opioid prescription within three days of being discharged from the emergency department (Table 3.4). Most prescriptions were

filled within one day following the index emergency department visit and no individuals were prescribed a long-acting opioid. The median average daily dose of the index prescription was 37.5 MME/day (IQR: 25.7-50); 32.7% of prescriptions filled were for an average of 50 MME/day or higher. The median days' supply of the index prescription was 3 (IQR: 2-5); 38.8% of prescriptions filled were for more than 3 days' supply.

Table 3.4. Characteristics of the index opioid prescription.

Characteristic	No. (%) of patients receiving a Rx n=49
Days to Rx fill, median (IQR)	0 (0-1) range: 0-3
Long-acting opioid received	0
Dose, oral MME/day, median (IQR)	37.5 (25.7-50) range: 5-100
Dose category	
<50 MME/day	33 (67.3)
≥50 MME/day	16 (32.7)
Days' supply, median (IQR)	3 (2-5) range: 1-30
Days' supply category	
≤3 days	30 (61.2)
>3 days	19 (38.8)

IQR, interquartile range; MME, morphine milligram equivalents; Rx, prescription.

3.4.5 Patterns of Opioid Exposure in the Emergency Care System

In total, 131 (29.4%) of 445 patients received opioids. Among these patients, we observed the following patterns of opioid exposure: 13 (9.9%) only received in the ambulance, 19 (14.5%) only received in the emergency department, 24 (18.3%) only received at discharge, 10 (7.6%) only filled a prescription, 21 (16.0%) received in the emergency department and at discharge, 13 (9.9%) received in the emergency department and filled an opioid prescription, five (3.8%) received opioids at discharge and filled an opioid prescription, and 14 (10.7%) received opioids in the emergency department and at discharge as well as filled an opioid prescription (Table 3.5).

Table 3.5. Patterns of opioid exposure among patients with low back pain who received opioids in the emergency care system.

Pattern	No. (%) of patients receiving opioids n=131
Ambulance only	13 (9.9)
ED only	19 (14.5)
Discharge only	24 (18.3)
Rx only	10 (7.6)
Ambulance + ED	NR
Ambulance + discharge	NR
Ambulance + Rx	NR
ED + discharge	21 (16.0)
ED + Rx	13 (9.9)
Discharge + Rx	5 (3.8)
Ambulance + ED + discharge	NR
Ambulance + ED + Rx	NR
Ambulance + discharge + Rx	0
ED + discharge + Rx	14 (10.7)
Ambulance + ED + discharge + Rx	NR

ED, emergency department; NR, not reportable (cell size less than 5); Rx, prescription.

3.4.6 Prolonged Opioid Use

There were 54 study participants (12.1%) who met the criteria for prolonged opioid use, defined as filling an opioid prescription 4-180 days after the index emergency department visit. Appendix 7 summarizes the demographic and clinical characteristics of the study sample by prolonged opioid use status. Using our alternative definition of prolonged opioid use, we found that 20 individuals (4.5%) filled an opioid prescription 91-180 days after their emergency department visit.

Patients who had any opioid exposure in the emergency department, any opioid exposure at discharge, or any opioid prescription fill were more likely to develop prolonged opioid use than patients without an exposure at that point (adjusted RR 2.36, 95% CI: 1.46-3.82; adjusted RR 2.62, 95% CI: 1.67-4.11; adjusted RR 2.30, 95% CI: 1.54-3.43; respectively). Compared to patients who did not receive opioids, patients who had two opioid exposures (adjusted RR 2.91, 95% CI: 1.67-5.06) and patients who had

three or four opioid exposures (adjusted RR 3.05, 95% CI: 1.44-6.50) in the emergency care pathway had a higher risk of prolonged opioid use after adjusting for important patient characteristics. Patients in the following opioid exposure groups also had increased risk of prolonged opioid use compared to the unexposed group: discharge/prescription (adjusted RR 2.27, 95% CI: 1.01-5.07); ambulance/emergency department + discharge (adjusted RR 2.81, 95% CI: 1.34-5.89); ambulance/emergency department + prescription (adjusted RR 2.61, 95% CI: 1.16-5.85); and ambulance/emergency department + discharge + prescription (adjusted RR 3.85, 95% CI: 1.87-7.92).

Table 3.6. Associations between patterns of opioid exposure for low back pain in the emergency care system and prolonged opioid use (filling an opioid prescription 4-180 days following the index emergency department visit).

Pattern	RR [95% CI]	aRR [95% CI]*
Any ambulance opioid exposure	1.35 [0.55-3.29]	0.94 [0.38-2.32]
Any ED opioid exposure	2.93 [1.89-4.56]	2.36 [1.46-3.82]
Any discharge opioid exposure	2.67 [1.71-4.18]	2.62 [1.67-4.11]
Any opioid Rx fill	2.81 [1.75-4.50]	2.30 [1.54-3.43]
Cumulative number of opioid exposures		
None	[ref]	[ref]
One	2.06 [1.03-4.12]	1.72 [0.88-3.39]
Two	3.15 [1.74-5.71]	2.91 [1.67-5.06]
Three or four	4.21 [2.09-8.48]	3.05 [1.44-6.50]
Combinations of opioid exposure		
None	[ref]	[ref]
Ambulance/ED	1.50 [0.55-4.05]	1.03 [0.42-2.51]
Discharge/Rx	2.19 [0.95-5.02]	2.27 [1.01-5.07]
Ambulance/ED + discharge	3.11 [1.53-6.29]	2.81 [1.34-5.89]
Ambulance/ED + Rx	3.81 [1.71-8.50]	2.61 [1.16-5.85]
Ambulance/ED + discharge + Rx	5.14 [2.60-10.16]	3.85 [1.87-7.92]

aRR, adjusted relative risk; CI, confidence interval; ED, emergency department; RR, relative risk; Rx, prescription.
Only 443 patients were included in the analysis; two were excluded due to missing data on dimensions of the Canadian Index of Multiple Deprivation: Atlantic region. Associations between each of the patterns of opioid exposure and prolonged opioid use were explored in separate models.
* Adjusted for age, availability of primary care provider, economic dependency score, ethno-cultural composition score, residential instability score, situational vulnerability score, length of stay, Canadian Triage and Acuity Scale score, responsibility for payment, and sex.

In secondary analyses, we found that patients with two or more opioid exposures across the emergency care system did not have increased risk of prolonged opioid use compared to patients with a single exposure. However, patients who received opioids at discharge and filled an opioid prescription, after also receiving opioids in the ambulance or emergency department, had increased risk of prolonged opioid use compared to patients who only received opioids in the ambulance or emergency department (adjusted RR 3.74, 95% CI: 1.49-9.39) (Appendix 8).

Sensitivity analyses using our alternative definition of prolonged opioid use resulted in associations with wide confidence intervals and no clear relationships with any of our exposure variables of interest, except for with any discharge opioid exposure (adjusted RR 2.80, 95% CI: 1.11-7.06). We were unable to analyze associations between certain patterns of opioid exposure and prolonged opioid use for our alternative definition due to small cell numbers (Appendix 9).

3.5 Limitations

There are several limitations in our study related to identification of the study population, opioid exposures, and study design. We only included a lookback period of six months to determine opioid-naïve eligibility. In addition, we considered an individual to be opioid-naïve if they lacked an opioid prescription fill; this definition does not account for patients who obtained opioids in-hospital, through diverted means, or from the illicit drug market. It is possible that some patients were misclassified and not truly opioid-naïve, which could have led to differences in opioid delivery in the emergency care system (e.g., higher doses, more exposures) and exaggerated associations between patterns of opioid exposure and prolonged opioid use.

We also cannot ignore the potential impact of the COVID-19 pandemic on study population selection. Public health messaging during the pandemic encouraged individuals to stay home as often as possible, and individuals could be apprehensive about accessing emergency care for fear of contracting COVID-19. Our study sample included 445 opioid-naïve adults who presented to the QEII ED with low back pain between April 9, 2020, and September 30, 2020. For comparison, we used data from a larger cohort of opioid-naïve adults presenting to the QEII ED with low back pain (see Appendix 3 for description of cohort) to examine the same 25-week period pre-pandemic. There were 475 and 477 patients who presented to the QEII ED with low back pain over the same period in 2018 and 2019, respectively, representing a drop of 6.3% from 2018 to 2020 and 6.7% from 2019 to 2020. Sharma et al. noted a 31% reduction in presentations for low back pain at three major metropolitan emergency departments in Australia between 2019 and 2020.[91] While this was a steeper reduction than we observed in our cohort, this could be attributed to differences in population density and severity of the pandemic between Halifax, Canada, and Sydney, Australia. The authors also noted a higher proportion of patients arriving by ambulance during the pandemic.[91] Therefore, we recognize that the COVID-19 pandemic may have altered the makeup of our study population or affected care of low back pain across the emergency care system.

In consultation with local emergency physicians, we individually defined opioid dispensing events in the Pyxis database as ‘delivered in the emergency department’ or ‘delivered at discharge’ by considering a patient’s most likely clinical trajectory. However, there is potential for misclassification of these dispensing events in either direction. Moreover, dispensing and prescription data are only a proxy for actual opioid

use. Patients may be sent home with opioids at discharge on a 'take as needed' basis or fill an opioid prescription but not consume the entire dose. The conversion of opioid doses to MME can also be inexact, particularly for parenteral opioids and less well-documented opioid types (e.g., fentanyl, tramadol), and many MME conversion factors are based on chronic pain management with opioids and were not determined in opioid-naïve populations. This could lead to an underestimation of the true dosage of opioids delivered to patients in this study.

Our retrospective cohort study is also susceptible to residual and unmeasured confounding. Most patients (n=351, 78.9%) were missing information on self-reported pain intensity; therefore, we adjusted our analyses for CTAS score instead of pain intensity. However, since pain intensity is a more granular measure than CTAS and may better capture the severity of a patient's low back pain, confounding by indication could have biased our results. In addition, several important variables were missing in our administrative data sets, including individual socioeconomic factors, medical or psychiatric comorbidities, other substance use behaviours, history of substance use, patient preferences for receiving opioids, and psychosocial characteristics; potentially resulting in an overestimation of our observed associations. The precision of the estimates was also limited by our small sample size. Finally, our findings may not translate to other painful conditions or to other countries and/or healthcare settings where attitudes toward opioid administration and prescribing, or emergency care management, differ.

3.6 Discussion

In this cohort of opioid-naïve individuals who presented to a Canadian emergency

care system with low back pain, we observed many different patterns of opioid exposure across four key points of emergency care management: ambulance, emergency department, discharge, and community pharmacy (following emergency department prescription). Emergency department, discharge, and community pharmacy exposures were each individually associated with prolonged opioid use, irrespective of other exposures. Compared to patients who did not receive opioids, patients who had two or more opioid exposures in the emergency care system had increased risk of prolonged opioid use. Patients who were administered opioids in the ambulance and/or emergency department, received opioids at discharge, and filled an opioid prescription from the emergency department had the highest risk of prolonged opioid use and were nearly four times more likely than unexposed patients to fill an opioid prescription 4-180 days post-visit.

Our findings are comparable to previous work examining the association of emergency department opioid prescribing with prolonged opioid use. Hoppe et al. found that opioid-naïve patients who filled an emergency department opioid prescription for an acute painful condition had 1.8 times higher odds of filling an opioid prescription one year after the index visit compared to patients not prescribed opioids.[13] In an acute occupational low back pain cohort, Lee et al. observed that filling an opioid prescription within two days of the emergency department visit was associated with a 29% increased risk of filling ≥3 opioid prescriptions in the 12 months post-onset of injury.[14] Finally, Heard et al. found that opioid prescription, compared to no opioids, was associated with increased risk of ongoing opioid use among opioid-naïve patients discharged from the emergency department with back pain (RR 2.1).[15] Our observed RR of 2.30 for prolonged

opioid use following an opioid prescription fill, compared to no opioid prescription fill, is in line with these previous estimates.

Our results also suggest that emergency department opioid administration contributes to increased risk of prolonged opioid use. Similar to Heard et al., who found that patients who were only administered opioids in the emergency department had 1.9 times higher risk of ongoing opioid use at six months compared to those who did not receive any opioids,[15] we observed an increased risk of prolonged opioid use among patients who received opioids in the emergency department versus not (RR 2.36). In addition, we found that patients who received opioids at discharge and/or filled an opioid prescription after also receiving opioids earlier during the emergency care stay (ambulance/emergency department) had higher risks of prolonged opioid use. This observation aligns with Heard et al., who found that opioid administration plus opioid prescription was associated with increased risk of ongoing opioid use (RR 2.3).[15] Unique to our study, we observed that patients who received opioids in the ambulance/emergency department, at discharge, and filled an emergency department opioid prescription were more likely to develop prolonged opioid use than patients who only received opioids in the ambulance/emergency department, further suggesting that harms may compound in patients with multiple opioid exposures in the emergency care system.

Opioids have been a longstanding cornerstone of acute pain management. Our study provides new evidence that multiple opioid exposures across different stages of emergency care management may act together to further increase the risk of prolonged opioid use. Importantly, this work may inform the harmonization of opioid delivery practices within the emergency care system and contribute to successful opioid

stewardship practices in emergency medicine. Emergency care providers have an opportunity to re-evaluate their opioid delivery practices at the point of care, particularly when considering providing patients with a blister pack of opioids or an opioid prescription at discharge, based on opioids administered to patients earlier in the emergency care pathway.

With increasing evidence of harms following emergency department opioid administration or prescribing, there is a need for a prospective study to further interrogate the role of emergency care management as a possible gateway to prolonged opioid use and related harms. Additional research is required to determine whether the observed associations between certain patterns of opioid exposure (cumulative number of exposures, combinations of exposure) and prolonged opioid use may act through alternative mechanisms. For instance, the cumulative dose of opioids received by a patient may explain the relationship (i.e., more exposures = higher dose) or may interact with the total number of opioid exposures to meaningfully influence prolonged opioid use outcomes. The agreement between opioid dispensing events recorded in the Pyxis database and medication administration records in patient charts should also be investigated.[92] While automated medication dispensing systems contain potentially valuable data for research, these data are currently not easily accessible and their benefits and limitations have not been explored in depth.

In summary, opioid-naïve adults presenting to the emergency care system with low back pain had varying patterns of opioid exposure. Patients who received opioids were more likely to fill an opioid prescription 4-180 days after their index visit, and this risk was increased among patients with multiple exposures. Healthcare providers should

exercise caution when administering or prescribing opioids in the emergency care setting.

3.7 Acknowledgements

Portions of the data used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research/health service assessment analysis is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

CHAPTER 4 – CONCLUSION

4.1 Summary of Findings

The overarching objective of this study was to understand the totality of opioid exposure in the emergency care system and to explore potential pathways of subsequent prolonged opioid use within the low back pain population. Prior to this study, there was limited research about how opioids are delivered in emergency care settings, including opioid types, quantities, and routes of administration. In addition, previous studies have not described the different ways or combinations in which people can receive opioids across multiple stages of emergency care management, and whether these differences are important for developing prolonged opioid use. Importantly, no studies in Canada have investigated the association between opioid exposures within the emergency care setting and prolonged opioid use.

This study contributes new evidence about the characteristics of opioids being delivered in the ambulance, in the emergency department, and at discharge from the emergency department. This research also comprehensively describes patterns of opioid exposure for low back pain across the entire emergency care system. Finally, I identified several patterns of opioid exposure (both individual exposures and multiple/combination exposures) that were associated with an increased risk of prolonged opioid use. Altogether, the findings from this study highlight the interconnected nature and potential implications of opioid-related pain management within the emergency care setting.

4.1.1 Objective 1

The first objective of this thesis was to describe the characteristics of opioids delivered to opioid-naïve adults with low back pain as they transition through a Canadian

emergency care system. The results, from a Nova Scotia tertiary care centre in 2020, indicated that 41.7% of patients who arrived to the QEII ED by ambulance for low back pain received opioids while under the care of paramedics, with most patients receiving fentanyl. In the ambulance, the median dose of opioids delivered was 30 MME and the median number of opioid administrations was three. In the emergency department, 17.1% of patients were administered opioids during their visit. Most patients received oral opioids and hydromorphone was the most common type of opioid delivered in the emergency department. The median dose of opioids delivered in the emergency department was 10 MME and the median number of opioid administrations was one. At discharge, 15.7% of patients received opioids, and hydromorphone was again the most common opioid distributed at discharge. The median number of tablets sent home with patients was four. Finally, 11.0% of patients filled an opioid prescription within three days following their emergency department visit. All prescriptions filled were for a short-acting opioid, and the median dose and days' supply were 37.5 MME/day and three, respectively. I also found that 32.7% of patients filled a prescription for ≥50 MME/day and 38.8% filled a prescription for greater than three days' supply.

4.1.2 Objective 2

The second objective of this thesis was to identify patterns of opioid exposure for low back pain in the emergency care system. I described these patterns across four key points of emergency care management: the ambulance (including all stages of paramedic care), in the emergency department, at discharge from the emergency department, and a prescription fill at the community pharmacy likely attributed to an emergency department prescription. In total, I found that 29.4% of patients received opioids. Among these

individuals, the most commonly observed patterns of opioid exposure were: discharge only (18.3%); emergency department and discharge (16.0%); emergency department only (14.5%); emergency department, discharge, plus prescription fill (10.7%); ambulance only (9.9%); and emergency department plus prescription fill (9.9%). A smaller proportion of individuals only filled an opioid prescription (7.6%) or received opioids at discharge plus filled an opioid prescription (3.8%). The numbers of patients who received opioids (in the emergency department, at discharge, and/or filled an opioid prescription) after receiving opioids in the ambulance were less than five in all categories.

4.1.3 Objective 3

The third objective of this thesis was to investigate associations between patterns of opioid exposure for low back pain in the emergency care system and prolonged opioid use. I operationalized patterns of opioid exposure in six ways for analysis: any ambulance opioid exposure, any emergency department opioid exposure, any discharge opioid exposure, any opioid prescription fill, the cumulative number of opioid exposures, and the combinations of opioid exposure. I found that patients who received opioids in the emergency department, irrespective of other exposures, had 2.36 times higher risk of developing prolonged opioid use than patients who did not receive opioids in the emergency department (includes patients who did not receive any opioids as well as patients who received opioids but not in the emergency department). I found similar associations with prolonged opioid use for patients who received opioids at discharge versus those who did not receive at discharge (2.62 times higher risk), and for patients who filled an opioid prescription versus those who did not fill a prescription (2.30 times higher risk). For the cumulative number of exposures, I observed that patients who had at

least two opioid exposures across the four stages of emergency care management had a higher risk of prolonged opioid use compared to patients who did not receive any opioids. For the combinations of opioid exposure, patients with the following patterns of exposure were more likely to transition to prolonged opioid use than patients who did not receive opioids: discharge/prescription; ambulance/emergency department + discharge; ambulance/emergency department + prescription; and ambulance/emergency department + discharge + prescription.

In secondary analyses, I did not find any significant associations with the cumulative number of opioid exposures when setting the reference category as one exposure instead of none. However, the ambulance/emergency department + discharge + prescription group had a higher risk of prolonged opioid use even when compared to the ambulance/emergency department group. In other words, patients who received opioids in the ambulance and/or emergency department, at discharge, and filled an opioid prescription were more likely to fill an opioid prescription 4-180 days after their emergency department visit than patients who only received opioids in the ambulance and/or emergency department.

4.2 Strengths

This thesis has several major strengths. To my knowledge, this is the first study to collectively describe characteristics of opioids delivered across multiple points in the emergency care system (including the prehospital setting) and to identify patterns of opioid exposure among patients seeking treatment in the emergency care system. This study is also the first in Canada to quantify the risk of prolonged opioid use following a brief exposure to opioids in the emergency care system.

This foundational study has also successfully leveraged an existing yet underutilized data infrastructure. I conducted an extensive linkage of six data sources that, together, are ideally suited to track opioid exposure from point of care to the community pharmacy. By troubleshooting the data access and linkage process alongside local data managers and Health Data Nova Scotia, I gained valuable insight about what data existed, what data were accessible, and how data were operationalized; this will allow me to improve ease of use for future studies in Nova Scotia and Canada.

4.3 Challenges Encountered and Additional Limitations

I encountered several obstacles during the conduct of this work that may inform future research in this area and future studies utilizing similar data sets. First, I faced substantial challenges accessing Pyxis data for this research, which resulted in deviations from my protocol. Initially, I anticipated receiving data from all six databases of interest for the period covering October 28, 2016, to September 30, 2020. However, at the time of data extraction and linkage, it was determined that Pyxis data were only available for the period from April 9, 2020, to September 30, 2020. Though I was able to extend DIS coverage to March 31, 2021, to allow assessment of the prolonged opioid use outcome, the limited availability of Pyxis data had two major implications: 1) the study sample size was reduced from 3,357 to 445 eligible patients, and 2) the observation window to assess prolonged opioid use was reduced from 14 months, as per the original protocol, to six months (in order to ensure complete data for outcome measurement). Since the Pyxis data were required to assess opioid administration in the emergency department and at discharge, and were therefore a focal point of this study, I elected to proceed with the smaller sample size as opposed to moving forward without the Pyxis data.

The significantly reduced number of study participants necessitated that I modify the analytical plan. I originally planned to use latent class analysis to identify clusters of individuals with similar patterns of opioid exposure in the emergency care system (Objective 2). Latent class analysis is a mixture modeling tool in which subjects within a population are classified into mutually exclusive and exhaustive subgroups (classes) that cannot be measured directly but can be informed through a set of observed variables.[93] The purpose of latent class analysis is to identify the number of latent classes that optimally describe the multidimensional structure of the data present in the study sample. Though I attempted to use the latent class analysis approach with the sample of 445 patients, I was unsuccessful in achieving convergence for models with more than three classes, even after substantially simplifying the latent class model to only contain four dichotomous yes/no variables (opioids received in the ambulance, opioids received in the emergency department, opioids received at discharge, opioid prescription filled at the community pharmacy). Due to the limited success and usefulness of this approach with the smaller data set, I instead described all possible ways that a patient could be exposed to opioids in the emergency care system. For analysis, I then grouped patients in six different ways to explore associations between the six resulting exposure variables (any ambulance opioid exposure, any emergency department opioid exposure, any discharge opioid exposure, any opioid prescription fill, the cumulative number of opioid exposures, and the combinations of opioid exposure) and prolonged opioid use in separate models. I considered each exposure variable to be clinically relevant and potentially targetable for intervention. However, since these variables (and categorizations within each of the variables) were researcher-driven, as opposed to the data-driven approach of latent class

analysis, and have not been validated in previous studies, this approach may have introduced bias into the study.

In Section 3.5 of this thesis, I noted key limitations in this study related to identification of the study population, opioid exposures, and study design. This thesis was also limited by the definition of prolonged opioid use. First, I was only able to assess prolonged opioid use in the six months after the emergency department visit. Therefore, I was unable to assess some more commonly used measures of prolonged opioid use in the literature (e.g., three or more additional prescriptions filled in the year after the emergency department visit, or at least one opioid prescription filled within 60 days of one year after the index visit). Second, I hoped to capture continued opioid use in the study population by defining prolonged opioid use as filling an opioid prescription 4-90 days after the index emergency department visit and an additional prescription between 91-180 days after the index visit. This definition represents continued contact with the community pharmacy and ensures that the prescriptions are spread out (one within the first three months and another between four and six months). The timing of the intervals also increases the likelihood that the prescriptions are related to the initial low back pain indication; the first interval occurs close to the index visit and the second interval occurs soon after. However, only seven individuals (<2%) met these criteria, limiting my ability to perform any meaningful analyses. Therefore, I used a definition of prolonged opioid use that maximized study power (filling an opioid prescription 4-180 days after the index emergency department visit). I also performed sensitivity analyses with a commonly used definition of prolonged opioid use, filling an opioid prescription 91-180 days after the

index emergency department visit. However, only 4.5% of the study population met these criteria and the results were limited by small sample size.

Another important limitation is that Pyxis measures dispensed medications rather than medication administration. For example, an additional dose could be removed from the Pyxis machine if the drug was damaged somehow. The patient could also refuse the medication; therefore, medications may be returned to the machine or wasted. Alternatively, at discharge, patients may be sent home with opioids but told by the physician to only take the medication as needed. These scenarios would lead to an overestimation of the amount of opioids consumed by a patient in the emergency department or in the days following discharge.

It is also worth noting that the analysis was clustered by the emergency department healthcare provider that was linked to the index emergency department visit. In reality, patients come into contact with more than one provider during their visit (e.g., medical resident and staff physician, or several providers if the visit spanned multiple shift changes). Therefore, it is possible that the provider on record may not have been the provider that was responsible for administering or prescribing opioids. For longer visits, different providers could have ordered opioids as the visit progressed. We were unable to explore these potential scenarios in our study as we did not have any information on provider characteristics.

Finally, nearly 80% of patients were missing information on self-reported pain intensity upon emergency department presentation. While I had hoped to adjust the analysis for pain intensity (it is more granular than CTAS and better captures a patient's self-reported pain experience), I chose to adjust for CTAS score instead given the extent

of missing data for the pain intensity variable. Though no reason was given for the disproportionate missingness in this variable (all other patient clinical characteristics had complete information available), the data may be missing due to procedural reasons (i.e., changes in staff or processes) or different priorities amidst the COVID-19 pandemic.

4.4 Implications

Although exploratory in nature, this research offers preliminary evidence that may support improved opioid stewardship and harmonization of opioid delivery practices in the emergency care system for opioid-naïve patients seeking treatment for their low back pain. Relevant stakeholders include paramedics, emergency physicians, and other healthcare providers who encounter adults with low back pain in the emergency care setting, as well as local and provincial administrative health professionals and policy makers.

My finding that multiple opioid exposures for low back pain in the emergency care system compound to increase the risk of prolonged opioid use is particularly informative for clinical decision-making at the point of care. Though the mechanism through which this occurs needs to be explored in future studies, paramedics should consider a judicious approach to administering opioids for low back pain in the ambulance. Emergency physicians and other healthcare providers should also exercise caution when administering or prescribing opioids in the emergency department, since baseline exposures to opioids in the emergency department, at discharge, or at the community pharmacy via an emergency department prescription fill were shown to increase the risk of prolonged opioid use. Clinicians should pay particular attention at discharge when making decisions to provide patients with a blister pack of opioids and/or

an opioid prescription, based on the finding that patients who receive both (after also receiving opioids in the ambulance/emergency department) are more likely to fill an opioid prescription 4-180 days after their emergency department visit than patients who only received opioids in the ambulance/emergency department. While the findings of this thesis offer an opportunity to re-examine opioid delivery practices at the point of care, evidently the need for appropriate opioid provision should be balanced against the need for healthcare providers to provide patients with adequate management for their acute pain. Moving forward, I anticipate the discharge process to become an important checkpoint for successful opioid stewardship within the emergency care system.

My results may also be useful to local and provincial administrative health professionals and policy makers. Provincially, first opioid prescriptions have been prioritized for improvement by the College of Physicians and Surgeons of Nova Scotia (Strategic Plan: 2019-2020) and the Nova Scotia PMP (Strategic Plan: 2017-2020).[57,94] I found that 11.0% of the opioid-naïve study population filled an opioid prescription that was presumed to have originated from the emergency department, and that 32.7% and 38.8% of these prescriptions were for ≥50 MME/day and for greater than three days' supply, respectively. Current guidelines recommend that opioid prescriptions of three days or less will often be sufficient and that clinicians should use caution (carefully consider individual risks and benefits) when increasing dosage to ≥50 MME/day.[11] Therefore, this is an area that could be prioritized for improvement at the local and provincial level; for example, through quality improvement initiatives that seek to understand reasons for emergency department opioid prescribing above these thresholds.

This study has also improved our understanding of new opioid prescribing by contributing data on patterns of opioid exposure in the prehospital and emergency department settings leading up to an initial opioid prescription fill. Though several studies have now demonstrated an association between emergency department opioid prescribing and prolonged opioid use,[13–15] I urge policy makers and administrators to consider opioid prescribing in tandem with earlier opioid exposures in the emergency care pathway. For instance, an opioid-naïve patient with low back pain who fills an opioid prescription from the emergency department is likely to be functionally distinct from a patient who fills an emergency department opioid prescription after receiving several doses of opioids in the emergency department. Therefore, it is important to tease out these differences prior to developing and implementing new opioid prescribing policies.

4.5 Future Research

I have identified numerous potential avenues for future research. First, there is a clear need for a mixed-methods study that follows patients prospectively to better understand the complex nature of opioid exposure for low back pain across the emergency care system, including patient and provider experiences, and opioid use outcomes. One important aspect that I was unable to capture in this study is whether prolonged opioid use was truly an unintended outcome. For instance, it is possible that the emergency physician intended for a particular patient to transition to prolonged opioid use as part of their individualized treatment plan. Gathering this information through qualitative methods at the time of the emergency department visit will help provide a more complete picture of reasons for transitioning to prolonged opioid use. In addition to

measuring prolonged opioid use through administrative drug monitoring data, collecting patient-reported outcomes (e.g., self-reported consumption, reasons for use, pain intensity, opioid misuse) or data on other opioid-related harms (e.g., opioid-related hospitalizations or overdoses, opioid use disorder) would also provide more context to prolonged opioid use outcomes.

Another priority area for future research is exploring the mechanisms by which certain patterns of opioid exposure increase the risk of prolonged opioid use. My study found that patients who received opioids at multiple points in the emergency care process were more likely to develop prolonged opioid use. However, an important question arising from this finding is whether this relationship can be explained by the cumulative dose of opioids that a patient receives across the emergency care system (i.e., is it truly the number of opioid exposures that matters, or do more exposures simply mean that a patient is receiving a higher dosage?). There may also be an interaction between the cumulative number of exposures and the cumulative dose of opioids that would be useful to explore.

A future study should also investigate the agreement between opioid dispensing events recorded in the Pyxis database and the medication administration record. Such research would provide valuable information about the accuracy and usefulness of automated medication dispensing system data as a proxy for actual opioid administration. A 2010 study at a tertiary care pediatric facility in Nova Scotia found substantial agreement between the medication administration record and the dispensation record of the automated dispensing device for salbutamol by inhalation (kappa 0.71, 95% CI: 0.67–

0.75); however, discrepancies were noted.[92] It is possible that higher agreement would be observed for opioid medications, which are controlled substances.

Finally, my study was based at a single academic tertiary care emergency department in Nova Scotia. It would be meaningful to explore whether patterns of opioid exposure for low back pain differ in community emergency departments, and whether there are different associations between patterns of opioid exposure and prolonged opioid use in urban versus rural emergency department settings.

4.6 Significance

Overall, this thesis provides a meaningful snapshot of opioid exposure for low back pain in the emergency care system. I used rich and underutilized data sources to fill important evidence gaps and address provincial health priorities. This work will also allow me to share previously fragmented data with local EHS and emergency department administrators. The findings could inform clinical decision-making at the point of care, lay a strong foundation for future studies to utilize these data sets, and ultimately contribute to the larger goal of mitigating opioid-related harms for patients locally and nationally.

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Appendix 1 – The RECORD Statement

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 25-26	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 25
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 26-27		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 27		
Methods					
Study Design	4	Present key elements of study	Pages 27-28		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
		design early in the paper			
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 27-29		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give	Page 28	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the	Page 28, Appendix 2

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
		matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Pages 30-33	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Pages 30-33, Appendices 4-6
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 29-33		
Bias	9	Describe any efforts to address potential sources of bias	Page 33		
Study size	10	Explain how the study size was arrived at	Page 28		
Quantitative	11	Explain how	Pages 30-		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
variables		quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	33		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Pages 33-34		
Data access and		..		RECORD 12.1:	N/A

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
cleaning methods				Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 29
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and	Page 34, Figure 3.2	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by	Page 34, Figure 3.2, Appendix 3

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
		analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Pages 34-39, Tables 3.2-3.5, Appendix 7		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of	Page 39		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
		outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Pages 39-40, Table 3.6		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page 41, Appendices 8-9		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Pages 43-44		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 41-43	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 43
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 43-47		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 43		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article	Page ix		

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
		is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	N/A

Appendix 2 – Eligible Low Back Pain Population

Step 1: QEII ED chief complaint of 'back pain' or 'traumatic back/spine injury' **Step 2:** ICD code indicating non-specific low back pain or mechanical/radicular low back pain at discharge		
Non-specific low back pain (previous published studies)		
724.2	Recurrent low back pain	ICD9
724.5	Back pain	ICD9
724.5	Chronic back pain	ICD9
724.5	Pain - back nyd	ICD9
724.6	Pain sacrum	ICD9
724.79	Pain coccyx	ICD9
724.8	Facet joint syndrome	ICD9
729.1	Musculoskeletal pain	ICD9
729.82	Muscle cramp	ICD9
729.9	Other msk	ICD9
Non-specific low back pain (consensus process)		
715.9	Osteoarthritis	ICD9
719.45	Pain - hip nyd	ICD9
719.49	Polyarthralgia	ICD9
720.2	Sacroiliitis	ICD9
721.3	Sacroiliac arthritis	ICD9
724	Unspecified back disorder	ICD9
724.6	Disorders of sacrum (ankylosis or instability of lumbosacral/ sacroiliac joint)	ICD9
724.6	Pain buttock	ICD9
724.7	Disorders of coccyx	ICD9
729	Other disorders of soft tissues	ICD9
729.9	Other msk	ICD9
780.9	Chronic pain (misc)	ICD9
843.8	Strain gluteal muscle	ICD9
843.9	Sprain hip	ICD9
844.8	Strain hamstring	ICD9
846.9	Unspecified	ICD9
847	Sprain/strain back	ICD9
847.2	Lumbar	ICD9
847.3	Sacrum	ICD9
847.4	Coccyx	ICD9
847.9	Unspecified	ICD9
848	Other and ill-defined sprains and strains	ICD9
848.8	Other sprain/strain trunk	ICD9
848.9	Unspecified site	ICD9
959	Injury, other and unspecified	ICD9
959.1	Trunk injury	ICD9
959.19	Other site on trunk	ICD9
959.8	Other specified sites, including multiple	ICD9
998.1	Bruising (po)	ICD9
M13.9	Arthritis, unspecified	ICD10
M25.5	Joint pain	ICD10

M54.5	Back pain	ICD10
M62.6	Muscle strain	ICD10
M79.1	Myalgia	ICD10
M81.9	Osteoporosis	ICD10
S30.8	Superficial inj low back/pelvis	ICD10
S31.0	Ow lower back/pelvis, uncomplicated	ICD10
V71.8	Normal exam	ICD10
Z71.9	Counselling/medical advice	ICD10
Mechanical/radicular low back pain (previous published studies)		
721.3	Spondylosis lumbar spine	ICD9
721.9	Arthritis back	ICD9
721.9	Osteoarthritis back	ICD9
722.1	Herniated lumbar disc	ICD9
722.2	Herniated disc (neuro)	ICD9
722.6	Degenerative disc disease	ICD9
724.2	Mechanical low back pain	ICD9
724.2	Recurrent low back pain	ICD9
724.3	Sciatica	ICD9
724.8	Muscle spasm back	ICD9
724.9	Ankylosis spine	ICD9
729.1	Musculoskeletal pain	ICD9
729.1	Myalgia	ICD9
729.2	Neuralgia	ICD9
729.2	Radiculopathy	ICD9
729.2	Radiculopathy leg	ICD9
846	Lumbosacral strain	ICD9
846.1	Sprain sacroiliac jnt/ligament	ICD9
847.2	Low back strain	ICD9
Mechanical/radicular low back pain (consensus process)		
722	Intervertebral disc disorder	ICD9
722.52	Degenerative disc disease	ICD9
722.93	Other and unspecified disc disorder (lumbar)	ICD9
724.0	Spinal stenosis	ICD9
728.9	Weakness leg	ICD9
733.13	Compression fracture, not due to trauma	ICD9
782.0	Paresthesia, nyd	ICD9
846.0	Lumbosacral joint or ligament	ICD9
846.2	Sacrospinatus (ligament)	ICD9
846.3	Sacrotuberous (ligament)	ICD9
846.8	Other specified sites of sacroiliac region	ICD9
M48.0	Spinal stenosis	ICD10
R20.8	Paresthesias - numbness	ICD10

Appendix 3 – Complete Description of Study Selection Process

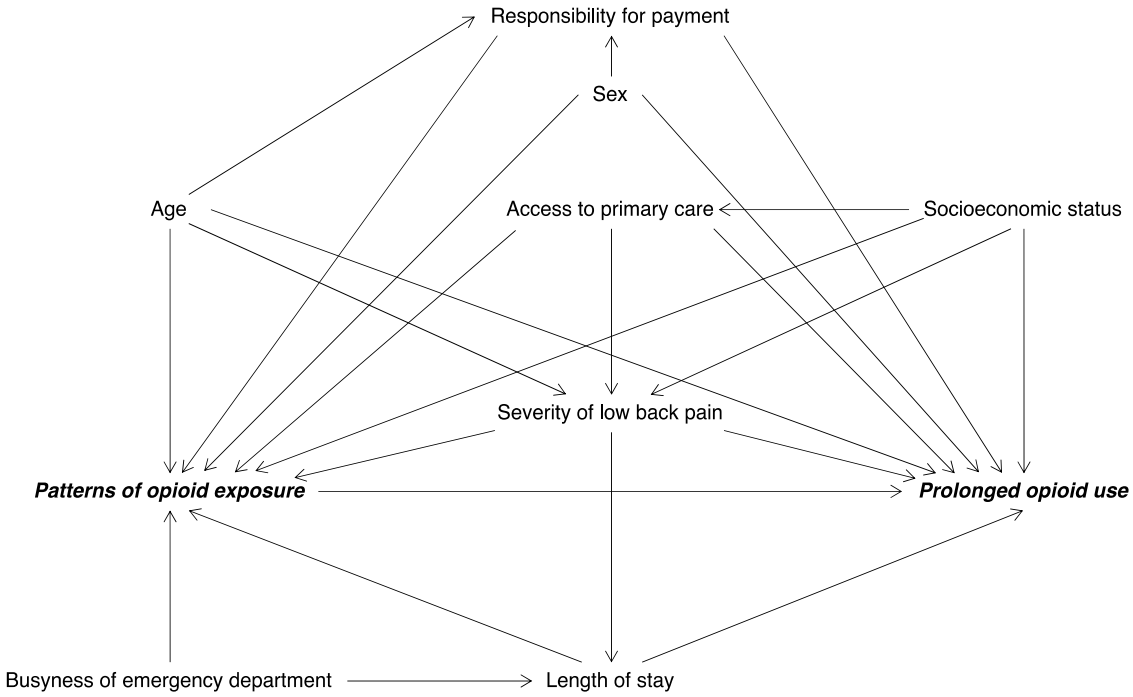
Our initial cohort consisted of opioid-naïve adults who presented to the QEII ED with low back pain between April 29, 2017, and September 30, 2020 (DIS coverage spanned from October 28, 2016, to March 31, 2021, to allow a six-month lookback period for assessment of opioid-naïve eligibility and a six-month follow-up period for assessment of prolonged opioid use). We received complete data from the EHS, EDIS, DIS, MASTER-POSTAL, and CIMD-A databases for this period. However, following data access and ethics approvals, Pyxis data were only retrievable for the period spanning April 9, 2020, to September 30, 2020. Therefore, our study was limited to patients who presented to the QEII ED between these dates, substantially reducing our sample size from >3,000 individuals to 445 individuals.

Importantly, opioid-naïve eligibility was determined based on a patient's index (first) emergency department visit between April 29, 2017, and September 30, 2020. Any subsequent emergency department encounters for a patient over that period were excluded. Since our study only included participants who presented during the period that Pyxis data were available (April 9, 2020, to September 30, 2020), our study sample may appear more opioid-naïve compared to the larger cohort (i.e., a patient could have been excluded from the larger cohort for filling an opioid prescription within six months before their index visit, but could have had a subsequent visit within the current study period with no opioid prescription fill in the six months prior). We expect that only a small number of participants were excluded from our study for this reason. Furthermore, this issue would likely bias the study results towards the null and underestimate the true associations.

Appendix 4 – Oral Morphine Milligram Equivalent Conversion Factors

Opioid type (in milligrams)	Oral morphine milligram equivalent conversion factor
Codeine	0.15
Hydromorphone	5
Morphine	1
Tramadol	0.17
Parenteral hydromorphone	15
Parenteral morphine	3
Parenteral or intranasal fentanyl	300

Appendix 5 – Directed Acyclic Graph



Appendix 6 – Potential Confounding Variables

Concept	Variable
Age	Age
Access to primary care	Availability of primary care provider
Socioeconomic status	CIMD-A dimension scores*
Length of stay	Length of stay
Severity of low back pain	Pain intensity, CTAS score†
Responsibility for payment	Responsibility for payment
Sex	Sex
Busyness of emergency department	Time of presentation‡

CIMD-A, Canadian Index of Multiple Deprivation: Atlantic region; CTAS, Canadian Triage and Acuity Scale.

* Economic dependency, ethno-cultural composition, residential instability, and situational vulnerability.

† We chose to adjust for CTAS score instead of pain intensity due to the substantial missingness in the pain intensity variable (see Table 3.2).

‡ Not included in the adjustment set based on the directed acyclic graph.

Appendix 7 – Patient Characteristics According to Prolonged Opioid Use Status

Demographic and clinical characteristics of the study sample according to prolonged opioid use status (filling an opioid prescription 4-180 days following the index emergency department visit).

	No. (%) of patients	
Characteristic	**No prolonged opioid use* n=391**	**Prolonged opioid use* n=54**
Demographic		
Age, yr, median (IQR)	45 (32-58) range: 18-91	57.5 (43-72) range: 19-94
Female sex	196 (50.1)	25 (46.3)
Availability of primary care provider	330 (84.4)	52 (96.3)
Responsibility for payment		
NS DHW	352 (90.0)	50 (92.6)
Workers' Compensation Board	39 (10.0)	NR
Economic dependency quintile		
Q1 (least deprived)	180 (46.0)	21 (38.9)
Q2	98 (25.1)	14 (25.9)
Q3	54 (13.8)	9 (16.7)
Q4	41 (10.5)	7 (13.0)
Q5 (most deprived)	16 (4.1)	NR
Missing	2 (0.5)	0
Ethno-cultural composition quintile		
Q1 (least deprived)	12 (3.1)	NR
Q2	17 (4.4)	0
Q3	31 (7.9)	NR
Q4	74 (18.9)	10 (18.5)
Q5 (most deprived)	255 (65.2)	39 (72.2)
Missing	2 (0.5)	0
Residential instability quintile		
Q1 (least deprived)	40 (10.2)	7 (13.0)
Q2	53 (13.6)	NR
Q3	35 (9.0)	NR
Q4	55 (14.1)	6 (11.1)
Q5 (most deprived)	206 (52.7)	35 (64.8)
Missing	2 (0.5)	0
Situational vulnerability quintile		
Q1 (least deprived)	160 (40.9)	28 (51.9)
Q2	84 (21.5)	12 (22.2)
Q3	65 (16.6)	NR
Q4	32 (8.2)	6 (11.1)
Q5 (most deprived)	48 (12.3)	5 (9.3)
Missing	2 (0.5)	0
Clinical		
Time of presentation		
Weekday	276 (70.6)	37 (68.5)
Working hours (M-F 8AM-5PM)	153 (39.1)	26 (48.2)

Characteristic	No. (%) of patients	
	No prolonged opioid use* **n=391**	**Prolonged opioid use*** **n=54**
Method of arrival		
Ambulance	52 (13.3)	8 (14.8)
Friend or relative	31 (7.9)	NR
Self	308 (78.8)	44 (81.5)
CTAS score		
1 (resuscitation)	0	0
2 (emergent)	32 (8.2)	9 (16.7)
3 (urgent)	274 (70.1)	38 (70.4)
4 (less urgent)	80 (20.5)	7 (13.0)
5 (non-urgent)	5 (1.3)	0
Pain intensity, NRS /10, median (IQR)†	5 (2.5-7) range: 0-10	1 (0-6) range: 0-8
Length of stay, hr, median (IQR)	3.3 (2.2-4.8) range: 0.6-19.8	4.0 (2.3-5.5) range: 0.9-23.8
Low back pain diagnosis		
Non-specific	259 (66.2)	38 (70.4)
Mechanical/radicular	132 (33.8)	16 (29.6)

CTAS, Canadian Triage and Acuity Scale; IQR, interquartile range; NR, not reportable (cell size less than 5); NRS, numeric rating scale; NS DHW, Nova Scotia Department of Health and Wellness.

* Percentages may not total 100 because of rounding.

† Missing n=351.

Appendix 8 – Secondary Analyses

Secondary analyses examining associations between patterns of opioid exposure for low back pain in the emergency care system and prolonged opioid use (filling an opioid prescription 4-180 days following the index emergency department visit).

Pattern	RR [95% CI]	aRR [95% CI]*
Cumulative number of opioid exposures		
None	0.49 [0.24-0.97]	0.58 [0.30-1.14]
One	[ref]	[ref]
Two	1.53 [0.72-3.24]	1.69 [0.80-3.56]
Three or four	2.04 [0.88-4.74]	1.77 [0.75-4.19]
Combinations of opioid exposure		
None	0.67 [0.25-1.80]	0.97 [0.40-2.36]
Ambulance/ED	[ref]	[ref]
Discharge/Rx	1.46 [0.46-4.62]	2.20 [0.72-6.75]
Ambulance/ED + discharge	2.07 [0.69-6.20]	2.73 [0.87-8.54]
Ambulance/ED + Rx	2.54 [0.85-7.57]	2.53 [0.96-6.67]
Ambulance/ED + discharge + Rx	3.43 [1.24-9.50]	3.74 [1.49-9.39]

aRR, adjusted relative risk; CI, confidence interval; ED, emergency department; RR, relative risk; Rx, prescription.

Only 443 patients were included in the analysis; two were excluded due to missing data on dimensions of the Canadian Index of Multiple Deprivation: Atlantic region. Associations between each of the patterns of opioid exposure and prolonged opioid use were explored in separate models.

* Adjusted for age, availability of primary care provider, economic dependency score, ethno-cultural composition score, residential instability score, situational vulnerability score, length of stay, Canadian Triage and Acuity Scale score, responsibility for payment, and sex.

Appendix 9 – Sensitivity Analyses

Associations between patterns of opioid exposure for low back pain in the emergency care system and prolonged opioid use (sensitivity analyses using an alternative definition of prolonged opioid use: filling an opioid prescription 91-180 days following the index emergency department visit).

Pattern	RR [95% CI]	aRR [95% CI]*
Any ambulance opioid exposure	-	-
Any ED opioid exposure	0.89 [0.29-2.74]	0.88 [0.26-2.95]
Any discharge opioid exposure	2.28 [0.92-5.67]	2.80 [1.11-7.06]
Any opioid Rx fill	1.43 [0.43-4.82]	1.48 [0.52-4.19]
Cumulative number of opioid exposures		
None	[ref]	[ref]
One	1.45 [0.45-4.64]	1.71 [0.47-6.28]
Two	0.55 [0.07-4.32]	0.60 [0.08-4.52]
Three or four	2.29 [0.51-10.35]	2.14 [0.44-10.44]
Combinations of opioid exposure		
None	-	-
Ambulance/ED	-	-
Discharge/Rx	-	-
Ambulance/ED + discharge	-	-
Ambulance/ED + Rx	-	-
Ambulance/ED + discharge + Rx	-	-

aRR, adjusted relative risk; CI, confidence interval; ED, emergency department; RR, relative risk; Rx, prescription.

- means model would not converge or was not interpretable.

Only 443 patients were included in the analysis; two were excluded due to missing data on dimensions of the Canadian Index of Multiple Deprivation: Atlantic region. Associations between each of the patterns of opioid exposure and prolonged opioid use were explored in separate models.

* Adjusted for age, availability of primary care provider, economic dependency score, ethno-cultural composition score, residential instability score, situational vulnerability score, length of stay, Canadian Triage and Acuity Scale score, responsibility for payment, and sex.