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Long-Term Opioid Prescribing among Patients Living with Metastatic Cancer as a Chronic Disease

by

Hannah Harsanyi

A THESIS

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Abstract

Patients living with metastatic cancer often experience pain which requires involvement of palliative care and symptom management teams. Opioids are a commonly used tool for the treatment of this cancer-related pain. While opioids serve an important purpose in symptom management and end-of-life care, harms related to their use are increasingly recognized as having a significant impact on patients with cancer. This changing perception has resulted from a growing body of literature investigating opioid-related harms, such as long-term prescribing, opioid-related healthcare utilization, and nonmedical use within cancer populations. However, many of these studies exclude patients with metastatic disease, and very few specifically investigate this population. The work reported in this thesis aims to address this knowledge gap by reviewing perceptions of opioid use among patients with metastatic disease, investigating the incidence of opioid-related hospitalizations and emergency department visits among recipients of long-term opioid prescribing, and determining the contribution of nonmedical opioid use to these encounters. Based on a review of previously published literature, stigmatization of opioid use was identified as a significant barrier to effective cancer pain management. Patients reported fears of addiction, tolerance, and side-effects which led to opioid-restricting behaviours. Despite these reported concerns, a large proportion of patients in Alberta received long-term opioid prescribing, with 23% of opioid-naïve patients with chronic metastatic disease being affected. Among these patients, the incidence of opioid-related healthcare encounters was higher than that reported in other cancer populations and was significantly associated with higher dosage and concurrent prescribing of psychoactive medications. Increased implementation of harm-reduction measures may be useful to mitigate this risk. From reviewing medical records of patients who experienced opioid-related healthcare encounters, nonmedical opioid use was identified as a possible contributing factor for 35% of patients. However, a majority of encounters were not primarily attributable to nonmedical opioid use and many patients experienced poorly controlled pain and displayed possible manifestations of opioid stigma. While risk assessment for nonmedical opioid use is important for patients receiving long-term opioid prescribing, it should be conducted in a non-stigmatizing manner which encourages patients to prioritize effective management of their pain.

Preface & Author Contributions

For this thesis, the following three manuscripts have been published or have been submitted for publication in peer-reviewed journals. Author contributions for each of the manuscripts are outlined below. The manuscripts are reproduced in their entirety in chapters 2-4 of this thesis, respectively. Permissions for inclusion of each paper have been obtained from copyright holders and co-authors of each paper where relevant (*Appendix 3*).

> Harsanyi, H.; Cuthbert, C.; Schulte, F. The Stigma Surrounding Opioid Use as a Barrier to Cancer-Pain Management: An Overview of Experiences with Fear, Shame, and Poorly Controlled Pain in the Context of Advanced Cancer. *Current Oncology.* 2023, *30*, 5835-5848. https://doi.org/10.3390/curroncol30060437
>
> Harsanyi, H.; Yang, L.; Lau, J.; Cheung, W.Y.; Xu, Y.; Cuthbert, C. Long-Term Opioid Prescribing and Related Hospitalizations or Emergency Department Visits among Patients with Metastatic Cancer: A Population-level Observational Study. (Submitted to *BMJ Supportive & Palliative Care*).
>
> Harsanyi, H.; Yang, L.; Lau, J.; Cheung, W.Y.; Cuthbert, C. The Contribution of Nonmedical Opioid Use to Healthcare Encounters for Opioid Poisoning and Use Disorders among Long-Term Users with Metastatic Cancer. (Submitted to *Supportive Care in Cancer*).

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The initial mystery that attends any journey is: how did the traveler reach his starting point in the first place?

-Louise Bogan

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List of Abbreviations and Acronyms:

ACR: Alberta Cancer Registry

ATC-code: Anatomical Therapeutic Chemical code

CAGE-AID: Cut down, Annoyed, Guilty, and Eye opener- Adapted to Include Drugs

CI: Confidence Interval

CRP: Cancer-Related Pain

DAD: Discharge Abstract Database

DSM-5: Diagnostic and Statistical Manuals of Mental Disorders, Fifth Edition

ED: Emergency department

EoL: End-of-Life

EMR: Electronic Medical Record

HREBA.CC: Health Research Ethics Board of Alberta, Cancer Committee

IASP: International Association for the Study of Pain

ICD-9: International Classification of Diseases, 9th edition

ICD-10: International Classification of Diseases, 10th edition

IQR: Interquartile range

IR: Immediate Release

IRR: Incidence Rate Ratio

LA: Long Acting

MAiD: Medical Assistance in Dying

mcg: microgram

MED: Morphine Equivalent Dose

MEDD: Morphine Equivalent Daily Dose

mg: milligram

NACRS: National Ambulatory Care Reporting System

NMOU: Nonmedical Opioid Use

NRS: Numerical Rating Scale

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

PIN: Pharmaceutical Information Network

OIH: Opioid-Induced Hyperalgesia

OR: Odds Ratio

ORT: Opioid Risk Tool

OSF: Opioid Stigma Framework

OUD: Opioid Use Disorder

QoL: Quality of Life

SD: Standard Deviation

SOAPP: Screener and Opioid Assessment for Patients with Pain

SOAPP-SF: Screener and Opioid Assessment for Patients with Pain, Short Form

WHO: World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Overview of Research Project

This thesis explores the role of opioids for treating patients living with chronic metastatic cancer, specifically investigating risks related to long-term opioid prescribing. Cancer causes substantial burden to people and the health system, with estimates that approximately 45% of Canadians will receive a cancer diagnosis in their lifetime.[1] People who are diagnosed with cancer, particularly those diagnosed with advanced disease, often experience cancer-related pain that can negatively impact their quality of life and physical functioning.[2] Managing this pain commonly requires the use of opioids, which are effective for pain and symptom management but do not come without risks.[3] Canada and the United States are currently experiencing an opioid epidemic related to over-prescribing, misuse, addiction, and overdose.[4] In therapeutic settings, long-term use of opioids has been associated with a variety of adverse outcomes, including the potential for patients developing tolerance, dependence, or toxicity.[5] These risks are poorly characterized among patients diagnosed with metastatic cancer and there remain unanswered questions about the optimal use of opioids for these patients.[6]

The research presented in this thesis addresses this knowledge gap by providing an overview of the current literature on this topic and presenting original research on long-term opioid prescribing and associated risks for patients who are living with metastatic cancer as a chronic disease. This work focused on several key areas related to opioid use for pain management among patients with metastatic cancer. First, a narrative literature review was used to describe patient and healthcare provider perceptions of opioid use, with a focus on how the opioid epidemic and stigmatization of opioids contributes to undertreatment and inadequate pain management. Second, long-term opioid prescribing practices and associated hospitalizations or emergency department visits were explored through a retrospective cohort study based on administrative health data. Third, the impact of nonmedical opioid use on the occurrence of opioid-related healthcare encounters was retrospectively assessed by reviewing medical records of patients who received long-term prescribing and subsequently experienced hospitalizations or emergency department visits related to opioid poisoning or opioid use disorders (OUDs). In the concluding section of this document, a synthesis of the evidence from this work in relation to clinical cancer care and current research activities is explored. This thesis provides information

relevant to advancing the state of the science about safe and effective opioid prescribing for patients living with metastatic cancer as a chronic disease.

1.2 Background

1.2.1 Metastatic Cancer Survivorship

Cancer metastasis is the process in which malignant cells spread from one part of the body to another and is a more advanced and difficult to treat form of disease.[7] Cancer is the leading cause of death in Canada[8] and a vast majority of cancer-related deaths are caused by metastases.[9,10] Metastatic disease is present among patients diagnosed with stage IV cancer (i.e., de novo metastatic disease) or those who develop a recurrence following treatment of their primary tumor.[10] Diagnosis at stage IV is common, occurring for approximately 50% of lung, 20% of colorectal, and 5% of breast cancer cases.[11] As a result, more than 200,000 Canadians are expected to be diagnosed with metastatic stage disease over the next five years.[11,12]

Patients who are diagnosed with metastatic cancer often have limited treatment options and are faced with the reality of living with cancer for the rest of their lives.[13] Due to the incurable nature of their disease, patients with metastatic cancer have a distinct survivorship experience which has previously been termed metavivorship.[14] In the traditional sense, survivorship referred to experiences of patients who have been deemed cancer-free and have completed curative-intent treatment.[15] However patients with de novo metastatic cancer exist entirely outside of this paradigm, receiving treatment which is primarily focused on maintaining quality of life (QoL), rather than eliminating or curing the disease. In this unique metavivorship space, patients may feel alienated from the classical narratives surrounding cancer care and face difficulties navigating how to live *with* cancer, as well as challenges associated with ongoing treatment where cure is not an option.[16]

In addition to coping with the incurable nature of their disease, patients with metastatic cancer have increased symptom burden and often face severe physical and psychological challenges.[13,17,18] The burdensome symptoms that co-exist with a diagnosis of metastatic cancer have led to the development of clinical guidelines which recommend early involvement of palliative care teams to lead more effective pain and symptom management for these patients.[19] Under this framework, palliative care is integrated with standard oncology care and co-occurs

with active disease treatment, rather than being initiated only in the terminal phase of the disease course.[20] Increased involvement of palliative care teams is further justified by shorter prognosis times, as five-year survival rates decrease with increased stage at diagnosis.[21] While patients with metastatic cancer continue to have survival rates significantly lower than that of patients with nonmetastatic cancer of the same type,[21] significant improvements have been made in the treatment of metastatic disease.[22] For patients with metastatic lung cancer, novel treatment options, including increased utilization of targeted therapies and immunotherapy, have led to a nearly five-fold increase in both two-year and five-year survival rates.[23] In metastatic breast cancer, 5-year survival rates have also drastically increased, jumping from 10 to 27% from 1985 to 2016.[24] Projections for all cancer types estimate a nearly 50% increase in the odds of 5-year survival for patients with metastatic cancer over the next 15 years, meaning that metavivorship is more and more likely to be a long-term experience for patients in the future.[22]

As a result of increased survival times, numerous patients diagnosed with metastatic cancer are now living with cancer as a chronic terminal disease. These patients and their experiences remain understudied and numerous calls to action have been issued to encourage greater research in this area.[14,16,25,26] Studies on metavivorship are needed in order to better understand differences between the metastatic and broader cancer population in terms of QoL, supportive care needs, and how to best provide care for patients living with cancer as a chronic incurable disease.

1.2.2 Cancer Pain and its Assessment

In 2020, the International Association for the Study of Pain (IASP) announced a revision to its definition of pain for the first time in more than forty years.[27] The new definition, which defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," aimed to better address the complexity of pain experience, which may have varying contributions from physical, psychological, and social components.[28] As a multidimensional, subjective experience, pain assessment relies on the use of self-reporting to classify pain in terms of its characteristics, duration, and severity.[29] Additional considerations may include physical investigations for pain aetiology, such as diagnostic imaging, as well as psychosocial assessments for potential modifiers of pain experience and pain

interference.[30] Accurate pain assessment and measurement is an essential component of creating a plan for pain management, as well as assessing the effectiveness of any pain treatment.[29,30]

Pain is one of the most common and troubling symptoms among patients diagnosed with cancer.[31] Not only is pain an "unpleasant experience," but it can have wide-ranging impacts on patients lives, effecting physical functioning, mood, sleep, and overall QoL.[32] Notably, about 2-in-3 patients with metastatic or terminal cancer report cancer-related pain, a prevalence nearly twice that of patients after curative-intent treatment.[33] Bone metastases are a common cause of pain for patients with metastatic disease, as they can lead to damage to the nervous system, inflammation, pathological fractures, or bone remodelling which results in debilitating pain.[34] Patients with metastatic disease may also experience pain from disease progression and malignant infiltration, pain associated with diagnostic or therapeutic procedures, or pain from other causes not directly attributable to cancer or its treatment.[35,36]

Cancer pain has varied presentations which should be comprehensively assessed when creating a plan for pain and symptom management.[31] In addition to cause, cancer pain can be categorized based on pathophysiology as being nociceptive, neuropathic and/or nociplastic depending on its description and aetiology.[35] Nociceptive pain, which includes categories of visceral and somatic pain, is commonly described as aching or throbbing, in contrast to neuropathic pain which is associated with nerve damage and is commonly described as a burning or electrical sensation.[37–39] Nociplastic pain, defined by the IASP as resulting "from altered nociception despite no clear evidence of actual or threatened tissue," was proposed as a third category which describes patients with conditions such as fibromyalgia and nonspecific chronic low back pain, which do not currently have a specific identifiable structural pathology.[40] In addition to pathophysiology, pain can be categorized as acute or chronic based on it's duration,[41] and may be complicated by breakthrough pain wherein patients experience transient episodes of increased pain from their baseline level.[42] Finally, pain can be assessed based on intensity, commonly using a 11-point numerical rating scale (NRS) from 0 to 10, where pain is categorized as none (NRS score 0), mild (NRS score 1-4), moderate (NRS score 5-6), or severe (NRS score 7-10).[43]

Due to various and often concurrent characteristics and aetiologies, cancer pain is difficult to accurately assess and treat. As a result, pain undertreatment is common, with nearly 40% of patients with cancer reported to receive inadequate analgesic treatment based on their

pain intensity.[44] Furthermore, as patients near the end-of-life (EoL) they often face disease progression and worsening symptoms which lead to high rates of severe pain.[45] Therefore, there is a significant need for involvement of palliative care teams who are better able to address the complex pain management needs of patients with metastatic cancer that commonly overlap with EoL care.

1.2.3 Opioid Analgesics for Cancer Pain Management

While optimal pain management involves individualized assessment and commonly requires both pharmacological and nonpharmacological interventions, opioids are a key treatment option for the management of cancer pain. In a simplified tool for guiding the pharmacological treatment of cancer pain, the World Health Organization (WHO) depicted opioids as occupying the upper 2-levels of the 3-level analgesic ladder, being the first choice for treating moderate-to-severe cancer pain.[46] Although current WHO guidelines emphasize that the analgesic ladder is not a strict protocol nor a replacement for individualized pain management, the analgesic ladder is still recognized as a useful guide which remains commonly used.[46] Similar recommendations for the use of opioids in cancer pain management are outlined in other clinical guidelines, including the National Comprehensive Cancer Network,[47] American Society of Clinical Oncology,[48] and European Society for Medical Oncology,[49] which each elaborate on the important role of opioids in this setting.

Opioids are a class of drugs with broad spectrum analgesic properties that act by binding to opioid receptors which interact with neuronal structures to reduce the sensation of pain.[50] In numerous systematic reviews, opioids have been shown to be effective at reducing the experience of cancer pain.[51–53] Different opioid drugs have differential interactions with opioid receptors (mu, kappa, delta and nociceptin)[54] and can be classified as pure agonists, partial agonists, or mixed-mechanism drugs.[55] There are few differences reported for the relative efficacy of different opioids, although the strength of evidence for comparative efficacy is generally lacking.[52,56–60] While there is no evidence to uniformly select one opioid drug over another, prescribing may be informed by clinician experience, patient opioid history, cost, and availability.[55] The relative potency of opioid drugs and routes of administration can be compared using established equianalgesic dose conversions to morphine equivalent dose (MED).[55,61]

Opioid analgesics are commonly available in long-acting (LA) or immediate release (IR) formulations, and patients with persistent pain are commonly prescribed an around-the-clock LA analgesic, with IR doses which can be taken on an as-needed basis for breakthrough pain or during pain crises.

The goal of pain management is to provide pain control which enables patients to maintain acceptable QoL and functioning.[46] The use of opioids for treating cancer pain requires dose individualization wherein a starting dose is adjusted in order to balance analgesia and potential adverse effects; there is not a uniform formula for opioid requirements.[55] The WHO recommended starting dose for opioid initiation with oral morphine is 5mg every four hours.[46] Pure mu-agonists, such as morphine, do not display a ceiling effect and have continued analgesic benefit with dose escalation.[55] As a result, opioid dose can be titrated up to a dose which provides adequate pain control based on individual analgesic response and dose-limiting adverse effects.[55,62] While opioid dose varies based on individual factors, guidelines for chronic non-cancer pain have suggested a cut-off of 90mg,[63] 120mg,[64] or 200mg[65] morphine equivalent daily dose (MEDD) to define high opioid dosage. However within the scientific literature, there is variability in definitions for grouping patients based on dosage level and a cut-off of 100mg MEDD has commonly been used to define patients receiving high opioid dosage.[66–69]

While opioids are an essential medicine for cancer pain management and palliative care,[70] they are best utilized within a comprehensive management plan which includes other pharmacological and nonpharmacological strategies.[46] Other pharmacological or clinical interventions may include nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, and/or palliative radiation therapy.[46] Additionally, cancer-related neuropathic pain is less responsive to opioid therapy[71] and the use adjuvant medications, such as antidepressants or anticonvulsants, may be beneficial for its treatment.[46] Furthermore, the provision of non-pharmacological or psychological interventions may improve pain self-management, and are an essential component of a comprehensive pain management plan which aims to address both the physiological and psychological aspects of pain.[72] In multiple systematic reviews, nonpharmacological strategies such as physiotherapy,[73] acupuncture,[74] mindfulness-based interventions,[75] and other psychosocial interventions[72] have been shown to significantly improve patients' pain experience.

1.2.4 Risks Related to Opioid Use

The use of opioids has resulted in an epidemic of misuse, addiction and overdose across North America.[4] Since 2016, the Government of Canada has reported nearly 45,000 apparent opioid-toxicity deaths, with an average of 22 deaths per day in 2023.[76] While a majority of these deaths resulted from the use of illegal non-prescription opioids,[76] overprescribing in clinical settings is also a significant contributing factor to the opioid epidemic.[77]

The applicability of these concerns to cancer care has been debated, as pain undertreatment remains prevalent[44] and declines in opioid prescribing may represent a exacerbation of these issues rather than a correction of overly liberal prescribing.[78] Additionally, harms related to the opioid epidemic are thought to have a relatively small impact on cancer populations, as the rate of opioid-related deaths among patients with cancer is approximately 10 times lower than that among the general population.[79] As such, the management of cancer pain has largely been excluded from updated guidelines which aim at reducing opioid prescribing.[80] Although there are ongoing concerns about opioid access, stigma, and pain undertreatment,[78] an increasing number of studies have demonstrated that opioid-related harms, including long-term use, addiction, misuse, and toxicity, have a considerable impact on cancer populations.[81]

1.2.4.1 Long-Term Opioid Use

While opioids are shown to be effective analgesics for treating acute pain, there is a lack of evidence for the effectiveness of long-term opioid use, which is additionally associated with adverse consequences of overuse, misuse, and dependence.[82] In chronic noncancer pain settings, findings favoring the long-term efficacy of opioid therapy rely on very low quality evidence with limited applicability to diverse pain types.[83,84] In cancer settings, the evidence for long-term efficacy is even more limited.[82,85]

Concerns regarding long-term efficacy are interconnected with concerns regarding the development of opioid tolerance and/or opioid-induced hyperalgesia (OIH). Opioid tolerance involves the need for increased opioid dose in order to obtain the same analgesic effect, and extensive literature has investigated the neurobiological and pharmacokinetic factors that may explain this phenomenon.[86] Complicating assessment of opioid tolerance is the possibility of patients who develop OIH, which describes a state of hypersensitivity to painful stimuli related to long-term use.[86] In cancer settings, subsequent dose escalations over the course of long-term

therapy have been associated with disease progression and increased pain rather than tolerance and/or hyperalgesia,[87] however these outcomes require further investigation, particularly within the context of the opioid epidemic.

Another sequalae related to long-term opioid use is the development of dependence, wherein patients may experience withdrawal symptoms when discontinuing opioid therapy.[88] In addition to physical adaptations causing tolerance and dependence, long-term opioid use may lead to psychological dependence, also termed addiction or substance use disorder.[89] The Diagnostic and Statistical Manuals of Mental Disorders, Fifth Edition (DSM-5) criteria for diagnosis of OUD includes opioid tolerance and dependence, as well as cravings, desire for or unsuccessful efforts to control opioid use, and continued use despite knowledge of having a physical or psychological problem related to opioid use.[90] Among patients with chronic cancer pain, the prevalence of OUD is estimated to be approximately 8%.[91]

In addition to concerns about long-term efficacy and dependence, long-term opioid use can lead to other adverse outcomes including disruptions in sleep quality, increased risk of osteoporosis and fractures, increased infection susceptibility, and hypogonadism.[65] Additionally, long-term opioid use has been implicated in cancer progression and some evidence supports involvement of opioids in the formation of distant metastasis; however, the net effect of opioids on cancer progression is unclear and may depend on the type of opioid, dose, and cancer type.[92–95] Finally, long-term opioid use has been associated with an increased risk of overdose and healthcare utilization among patients with cancer.[96]

Taken together, the consequences of long-term opioid use and questions regarding long-term efficacy lead to the conclusion that these prescribing practices should be used judiciously and may not be appropriate or beneficial in many cases, even among patients with metastatic cancer. However, these concerns need to be balanced with the particularities of metavivorship, including high symptom burden, painful disease progression, and the need for EoL care.

Throughout the literature, long-term opioid use is inconsistently referred to using a different terminology, including persistent, prolonged, or chronic opioid use. In cancer settings, long-term opioid use has primarily been investigated among patients in post-operative settings or following curative-intent treatment.[97–103] Reported rates of new long-term opioid use among patients following curative-intent treatment range from 2 to 18%.[97–103] Definitions of long-term

opioid use from these studies have limited applicability to patients with metastatic cancer, as they commonly rely on index windows which are defined by a surgery or treatment date, which is not a meaningful reference point for patients with metastatic disease receiving palliative treatment(s). As such, long-term opioid use in this setting can be better defined as the receipt of a greater than 90-day supply of opioids allowing for up to a 30-day gap in supply, which has been used in both cancer and non-cancer popluations.[104,105] There are currently no studies which investigate the prevalence of long-term opioid prescribing among patients living with chronic metastatic cancer, despite indications that long-term use is more common among patients with advanced disease.[106]

1.2.4.2 Nonmedical Opioid Use

Despite their important role in treating cancer pain, opioids have sedative and addictive properties which dispose them to misuse.[107] Nonmedical opioid use (NMOU) refers to a variety of behaviours including the use of illegal non-prescription opioids, the use of opioids based on the feeling or experience they provide, or use of prescription opioids not as indicated, either through using another individual's prescription or the using one's own prescription outside of prescribed parameters.[66,67] In existing literature, NMOU is referred to in a variety of ways, including not-as-prescribed opioid use,[108] aberrant opioid use,[109] opioid misuse,[110] chemical coping,[111,112] or OUD.[91] Use of the NMOU term has been favored as it attempts to use non-stigmatizing language to describe these behaviours.[81] For patients being prescribed opioids for cancer pain, NMOU may include self-escalation of opioid dose, use of an alternate route of administration, opioid diversion (where an individual's prescription is stolen, sold, or used by another individual), or use for a purpose other than that prescribed, for example to reduce anxiety or psychological distress.[108,113]

In contrast to non-cancer settings where these opioid-related behaviours have led to efforts to reduce overprescribing, in cancer settings focus has shifted toward risk assessment for identifying patients disposed to NMOU. Established risk factors for NMOU, including tobacco use, alcohol use, history of substance dependence, and personal or family history of mental health, are common within cancer populations;[81] a recent meta-analysis estimated that nearly 1-in-5 patients with cancer pain are at high risk of NMOU.[91]

Comprehensive pain assessment and responsible opioid prescribing in this setting is now thought to include assessment of patients' risk of NMOU, in addition to pain characteristics like intensity and aetiology.[114] Commonly used tools for assessing the risk of NMOU include the SOAPP-SF (Screener and Opioid Assessment for Patients with Pain, Short Form),[115] the Opioid Risk Tool (ORT),[116] and CAGE-AID (Cut down, Annoyed, Guilty, and Eye opener- Adapted to Include Drugs) questionnaire.[117,118] Standard use of these tools can aid in identifying patients who are currently engaged in or are at increased use of developing NMOU behaviours. Rather than precluding the use of opioids for these patients, identification of patients at high risk of NMOU should lead to increased monitoring of opioid use behaviours, implementation of harm-reduction strategies, and provision of interdisciplinary care to address psychosocial distress.[119]Although these tools have been used in palliative care settings, they were not specifically developed for and have not yet been validated for oncology or palliative care populations.[118]

1.2.4.3 Other Opioid-Related Adverse Effects

In addition to their propensity for nonmedical use, the therapeutic use of opioids may cause adverse effects, such as constipation, somnolence, and/or nausea & vomiting.[120] Furthermore, opioid use may lead to an increased risk of delirium in patients with advanced cancer.[121,122] These adverse effects need to be considered in relation to the benefits of analgesia, in addition to management with dose adjustments and prophylactic treatments.[123] In the case of an opioid overdose, a person experiences excessive stimulation of opioid receptors causing respiratory and central nervous system (CNS) depression, which can result in lethargy, loss of consciousness, and even death.[124] Administration of naloxone, a competitive opioid receptor antagonist, can reverse opioid toxicity and is a safe and effective treatment for opioid overdose, although its use can cause withdrawal symptoms among long-term opioid users and will also counteract the analgesic properties of the opioid in patients with pain.[124]

While some opioid-induced adverse effects are very common, serious effects resulting in emergency department visits or hospitalization are rare, accounting for less than 1% of encounters among patients with cancer.[125,126] Despite being relatively uncommon, the rate of these events has been found to significantly increase over time.[125,126] There are currently no

studies which focus on patients with metastatic cancer and report on these opioid-related healthcare encounters.

1.2 Research Purpose

The overarching purpose of this research was to examine the patterns and consequences of long-term opioid prescribing in the provision of pain and symptom management for patients living with chronic metastatic disease. Several interrelated studies were carried out to address this overall purpose.

1.2.1 Objective 1: Overview of Perceptions of Opioid Use for Patients with Metastatic Cancer

The aim of the first study was to explore how perceptions of opioid use in cancer settings have been influenced by extensive publication of the opioid crisis. A non-systematic review of the literature was conducted to provide an overview of the crucial role of opioids for pain management and describe diverse patient and provider opinions on opioid use, as well as how they affect pain management decisions in the context of advanced cancer. The review focused on how opioid stigma acts as a barrier to optimal pain management for patients with metastatic cancer.

1.2.2 Objective 2: Long-Term Opioid Prescribing for Patients with Chronic Metastatic Disease from the Population Level

In the second study, a retrospective cohort study design was used to investigate long-term prescribing practices using population-based administrative health data. The purpose of this study was to identify patients receiving long-term opioid prescribing, characterize these patients and prescribing practices, and investigate how characteristics of long-term prescribing relate to the incidence of emergency department visits and hospitalizations related to opioid poisoning/overdose or OUDs. The duration of the long-term prescribing period, timing of opioid initiation, opioid dosage level, and concurrent prescription medications were considered as possible practices associated with an increased incidence of opioid-related healthcare encounters.

1.2.3 Objective 3: Nonmedical Opioid Use in the context of Long-Term Prescribing for Patients with Chronic Metastatic Disease

The aim of the third and final study in this thesis was to determine whether NMOU behaviours were identified as a contributing factor to the occurrence of opioid-related healthcare

encounters among recipients of long-term opioid prescribing. This retrospective study identified patients with chronic metastatic cancer who received long-term opioid prescribing and subsequently experienced a hospitalization or emergency department visit related to opioid poisoning/overdose or OUD. Medical records and clinician notes were used to follow patients and identify any documentation of NMOU behaviours. A narrative synthesis was used to describe the opioid-related healthcare encounters and factors reported as contributing to their onset. Statistical analyses were used to investigate the patient characteristics significantly associated with NMOU behaviours.

1.3 Thesis Outline

Contained in this manuscript-based thesis document are three papers which are published or submitted for publication in peer-reviewed journals. The first provides an overview of perceptions of opioid use in this setting, followed by two original research papers. These manuscripts are followed by a discussion of key findings, implications for clinical care, and recommendations for future research directions.

Relevant background information for this work is presented in Chapter 1.2, with specific attention to the unique survivorship experiences of patients with metastatic cancer (Chapter 1.2.1), the management of cancer-related pain in this setting (Chapter 1.2.2 & 1.2.3), and the potential risks related to opioid use (Chapter 1.2.4). The knowledge gap being addressed in this thesis is presented in Chapter 1.3, which outlines the aims of each section.

Chapters 2, 3, and 4 represent the main body of the thesis and are each comprised of a journal article. Chapter 2 contains a narrative literature review of the stigma surrounding opioid use and its impact on patients with metastatic disease; this article has been published as an open-access article in *Current Oncology* as of June 2023. The findings from this review highlighted some of the gaps in knowledge regarding optimal opioid prescribing of patients with metastatic cancer and provided key contextual information regarding complexities when balancing risk assessment for opioid prescribing and encouraging optimal pain management. Chapter 3 uses population-based administrative health data to identify patients receiving long-term opioid prescribing and investigate the incidence of opioid-related healthcare encounters; this manuscript has been reviewed by all co-authors and has been submitted to *BMJ Supportive & Palliative Care*. This

study led to the identification of patients who would be included in the subsequent chart review study and provided information on the prevalence of these issues in the study population. Finally, Chapter 4 provides a detailed description of opioid-related healthcare encounters and investigates NMOU behaviours among these patients. This manuscript has been reviewed by all co-authors and submitted to *Supportive Care in Cancer* for consideration. These articles are subject to changes due to the peer-review process required for their future publication.

Chapter 5 is the concluding chapter of this thesis, which presents a discussion of the role of opioid use for managing cancer pain among patients with chronic metastatic disease. This discussion was jointly informed by existing clinical guidelines, previously published literature, and the findings presented in this work. Key findings of the thesis are outlined in Chapter 5.1. Limitations of this work and challenges related to studying opioid use for patients with metastatic cancer are discussed in Chapter 5.2. Finally, recommendations for clinical practice and future research are presented in Chapters 5.3 and 5.4, respectively.

The manuscript-based format of this thesis means that some of the information presented in each chapter may be repeated in other chapters. The research conducted for this thesis was completed through the collaborative efforts of many people; author contributions for each study are provided in the preface of this thesis along with full citations for each manuscript. Copyright holder permissions, co-author permissions, and supplementary materials are located in the appendices of this document.

CHAPTER 2: LITERATURE REVIEW OF PATIENT PERSPECTIVES ON OPIOID USE

The Stigma Surrounding Opioid Use as a Barrier to Cancer-Pain Management: An Overview of Experiences with Fear, Shame, and Poorly Controlled Pain in the Context of Advanced Cancer.

2.1 Abstract

Cancer-related pain affects a majority of patients with advanced cancer and is often undertreated. The treatment of this pain is largely reliant on the use of opioids, which are essential medicines for symptom management and the maintenance of quality of life (QoL) for patients with advanced cancer. While there are cancer-specific guidelines for the treatment of pain, widespread publication and policy changes in response to the opioid epidemic have drastically impacted perceptions of opioid use. This overview therefore aims to investigate how manifestations of opioid stigma impact pain management in cancer settings, with an emphasis on the experiences of patients with advanced cancer. Opioid use has been widely stigmatized in multiple domains, including public, healthcare, and patient populations. Physician hesitancy in prescribing and pharmacist vigilance in dispensing were identified as barriers to optimal pain management and may contribute to stigma in the context of advanced cancer. Evidence in the literature suggests that opioid stigma may result in patient deviations from prescription instructions, which generally lead to pain undertreatment. Patients reflected on experiencing shame and fear surrounding their prescription opioid use and feeling uncomfortable communicating with their healthcare providers on these topics. Our findings indicate that future work is required to educate patients and providers in order to de-stigmatize opioid use. Through alleviating stigma, patients may be better able to make decisions regarding their pain management which lead to freedom from cancer-related pain and improved QoL.

2.2 Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage,"[1] demonstrating that pain is a complex biopsychosocial symptom. Cancer-related pain (CRP) affects more than 65% of patients with advanced cancer[2] and is one of the most common[3] and highest priority symptoms for these patients.[4,5] CRP impacts

multiple aspects of wellbeing, including physical, emotional, and interpersonal domains, and improper management can thereby have negative impacts, such as sleep disturbance, depression, distress, and diminished quality of life (QoL).[6] Manifestations of pain are not only physical, but are inextricably linked to patient perceptions, which are modulated by mood, culture, psychological wellbeing, and personal beliefs.[7,8] Due to the complex nature of CRP, the provision of appropriate pain management is a difficult task, but is essential for maintaining QoL for a majority of patients with advanced cancer.[9]

The population of patients with advanced cancer is largely understudied,[7] and these patients have unique needs as a result of facing incurable prognoses and living with cancer as a chronic disease. Over recent years, more advanced treatment options have allowed patients with terminal diagnoses to have significantly increased survival times.[7] For example, among young women with metastatic breast cancer, 5-year survival rates increased from 45.6% to 56.5% from 2005–2009 to 2010–2015, while survival rates remained relatively stable among women with non-metastatic disease over the same period.[10] In many cases, patients with advanced stage disease are now living with cancer and its effects for many years[11] and may experience prolonged existential burden, psychosocial distress, and physical symptoms as a result. Patients with advanced cancer commonly report high levels of depression, anxiety, and hopelessness,[12] in addition to physical symptoms including pain, nausea, fatigue, and dyspnea.[13]

The goal of treatment for these patients is generally palliative, focused on the alleviation of symptoms, rather than curative-intent. In these cases, the healthcare system's primary role is centered on providing symptom control and maintaining patient QoL throughout the disease trajectory. Due to a high prevalence of pain, coupled with increasing survival times and differing treatment priorities, barriers to effective symptom management are particularly impactful for patients with advanced cancer.[14] This paper therefore aims to provide an overview of the crucial role of opioids for pain management in the context of advanced cancer and explore how perceptions of opioid use in cancer settings have been influenced by extensive publication of the opioid crisis. Based on these findings, the review will provide considerations for clinical practice and future directions.

2.3 Methods

A narrative review was completed using keyword searches on PubMed, EMBASE, and Google Scholar. Keywords included ‘cancer’, ‘malignant’, ‘metastatic’, ‘advanced’, ‘opioid’, ‘pain’, ‘cancer-related pain’, ‘pain management’, ‘stigma’, and ‘opiophobia’. Included articles focused on perceptions of opioid use for the treatment of pain among patients with advanced cancer. Abstract-only and non-English articles were excluded.

2.4 The Role of Opioids in Cancer Pain

Opioids are considered to be a gold-standard therapy for cancer pain management, and the World Health Organization (WHO) recommends them as the first choice for the treatment of moderate-to-severe CRP.[15] Opioids act as analgesics by binding receptors on the nociceptive pathway and thereby reduce perception of pain at the somatosensory cortex.[16] Common opioid therapies used in the treatment of CRP include morphine, hydromorphone, oxycodone, codeine, and fentanyl. Opioid analgesics have been shown to be highly effective,[17,18] and are designated as essential medicines for palliative care.[19] Clinically meaningful alleviation of CRP can be achieved through opioid use in approximately 80% cases,[20] and while multimodal management strategies are needed for the remaining approximately 20% of cases,[21] opioid therapies are an indispensable resource for pain and symptom management among patients with cancer. Guidelines for the treatment of CRP recommend that opioids be prescribed to patients with moderate-to-severe pain, unless contraindicated, and should be prescribed at the lowest dose necessary to achieve adequate analgesia.[22] Additionally, clinical guidelines recommend that all patients with advanced cancer receive access to specialty palliative care services which has increased expertise and focus on pain and symptom management.[23] Despite these guidelines outlining the appropriate treatment of CRP, meta-analyses have demonstrated that more than 30% of patients with cancer are undertreated based on their pain severity.[24,25] While pain undertreatment appears to be less prevalent among patients with advanced disease, in studies including a majority of metastatic patients the rate of undertreatment remains high, affecting approximately 20% of patients.[24]

2.5 The Opioid Epidemic and Changes in Opioid Prescribing

North America is facing an ongoing opioid epidemic which poses one of the most challenging and pressing public health issues of our time.[26] The Government of Canada has reported more than 30,000 opioid toxicity deaths from 2016 to 2021, and a worsening of the

overdose crisis over time.[27] In recent years, numerous updated guidelines have been published with the intent of curbing the prescribing of opioids in response to high levels of non-medical opioid use (NMOU) and associated adverse effects.[28,29] However, it is important to note that these guidelines were not intended to impact patients experiencing CRP and were specifically established for the treatment of non-cancer pain.[30]

Despite the intended limited scope of updated guidelines, declines in opioid prescribing have been observed among oncologists in recent years,[31–34] and these declines have been particularly pronounced among patients with metastatic cancers. From 2011 to 2017, opioid prescriptions for patients with bone metastasis were found to decline significantly, in terms of both proportion of patients receiving prescriptions as well as dosage level.[33] It is difficult to determine if these changes represent an appropriate correction in over-prescribing by certain practitioners, greater reliance on alternative methods of pain management, or could represent a concerning exacerbation of issues of pain undertreatment.[35] What is clear is that the ongoing opioid epidemic has led to increased stigmatization regarding the use of opioids, with some research proposing two concurrent opioid epidemics: one resulting from illicit opioid use and overdose deaths, and another resulting from 'opiophobia', characterized by reduced access to opioids and fears relating to their use.[36]

2.6 What Are the Risks of Opioid Use among Advanced Cancer Patients?

There is a variety of evidence indicating that there are significant differences between cancer and non-cancer populations in terms of the risks of opioid use. The lifetime prevalence of opioid-use disorder among non-cancer patients prescribed long-term opioid therapy has been estimated at 41.3%,[37] compared to an estimated prevalence of 8% among patients with cancer-related chronic pain.[38] In terms of overdose deaths, there were 8.97 opioid deaths per 100,000 people among the general population in 2016, compared to 0.66 opioid deaths per 100,000 among cancer patients.[39] Given the differences between these populations, it is clear that prescribing practices or guidelines should not be extrapolated from the general population to patients with cancer. While there are differences between cancer and non-cancer populations, consideration of the risks related to opioid use is still relevant when prescribing opioids to cancer populations. Older literature from the 1980s to late 1900s suggest that NMOU among patients with cancer is low compared to the general population.[40,41] However, while commonly cited,

these studies are outdated and may no longer be relevant in the opioid epidemic era. A more recent review indicated that approximately 20% of patients with cancer are at high risk for opioid use disorder.[42] Similarly, a recent study of 1554 patients taking opioids for cancer pain found that 19% developed NMOU behaviours.[43] When specifically investigating patients with advanced cancers, a study found that 18% were diagnosed with chemical coping.[44] While there are a variety of metrics for evaluating NMOU which are difficult to compare, it is increasingly evident these issues are applicable to the cancer community, including those with advanced cancer.

Long-term opioid use, which may be a risk factor for NMOU,[45] has been defined as use of medically prescribed opioids for at least 90 days;[46] this outcome has not commonly been considered a concern for patients with advanced cancer given their historically short survival times. The significant increase in survival times among this population means that consideration of long-term use has become applicable, and studies on this topic are timely, if not overdue.[35,47] Among opioid-naïve patients after curative-intent surgery for cancer, the risk of new persistent opioid use has been estimated at approximately 10.4%.[48] There are no population-based estimates for the risk of long-term opioid use in patients with advanced cancer. The inability to provide patients with this information may lead to exaggerated fears regarding long-term opioid use, and the exclusion of these patients from studies may be damaging, rather than shielding, in terms of patient perceptions.

Further concerns for patients receiving opioid therapy include adverse effects such as the development of tolerance, physical dependence, cognitive dysfunction, constipation, and nausea.[49] While there are guidelines relating to the management of opioid-induced adverse effects among patients with cancer,[50–52] there is limited information on the incidence or prevalence of effects related to dependence and tolerance. The onset of adverse effects, as well as their potential for alleviation, are important considerations for patients, who need to weigh the tradeoffs between these symptoms, their impact on wellbeing and functioning, and the potential for experiencing freedom from pain.

In many cases, opioid dose escalations are required to maintain analgesic efficacy, which may be indicative of opioid tolerance or the pain hypersensitivity characteristic of opioid-induced hyperalgesia (OIH).[53,54] In cancer populations, the requirement for dose escalation is commonly attributed to disease progression, rather than increased tolerance or OIH.[55,56] While

many patients may experience increasing levels of pain as a result of disease progression, more research is needed to better understand the contribution of opioid tolerance and OIH in dose escalation and prolonged opioid use for patients with advanced cancer.[56]

An additional consideration for opioid prescribing to patients with cancer involves the immunomodulatory effects of opioids and their potential impact on disease progression or metastasis. The literature on the role of opioids in cancer remains contested, largely due to the complexity of the direct and indirect interaction of opioids with immune functioning, inflammation, and metastasis.[57] Long-term use and higher opioid dosages can reduce immune functioning and may impact its cancer-suppressing activity.[58] These risks require further research and review to elucidate the role of opioids in cancer promotion and suppression, as well as the clinical relevance of these effects.[59]

A lack of well-validated and specific information on the risks related to opioid use among patients with advanced cancer leaves patients and providers to guess and extrapolate regarding the trade-off between benefits and risks of opioid use. More research is required to understand these risks for patients with advanced cancer, as well as how they differ from broader cancer and non-cancer populations. This information could serve to alleviate uncertainty, which breeds fear and may be a contributor to stigmatization of opioids in this setting. The limited research on these outcomes means that implementation of a benefit-to-harm framework[60,61] may not be sufficiently informed for this population, and more work is needed to effectively implement risk assessment for patients with advanced cancer.

In recent years oncology-specific guidelines have encouraged careful risk assessment when prescribing opioids to patients with advanced cancer.[60,62–64] While the consideration of the risks of opioid use is important, assessment without interference from socioeconomic or racial biases poses a significant challenge to clinical oncologists. It has been demonstrated that physicians' implicit biases may lead to disproportionate pain undertreatment in vulnerable groups.[65–67] Risk assessment must therefore be carefully considered, and further developments which acknowledge the intrinsic biases with which providers approach shared decision-making opportunities are needed to improve these guidelines.

Risk assessment in this setting must additionally be considered with reference to issues of pain undertreatment. Under risk assessment recommendations, oncologists' assessment of risk

leads to a triage by risk process, wherein the clinician may opt to prescribe opioids, not prescribe opioids, or initiate opioids with risk-mitigation strategies and monitoring of drug-related behaviours.[63] Hesitancies in opioid prescribing may result from risk assessment which is not properly informed by a benefit-to-harm framework and may be influenced by stigma. A strong emphasis on risk assessment or mitigation, particularly without well-validated information among patients with advanced cancer, may act to further stigmatize opioid use, and act as a barrier to pain management in a population which is already subject to pain undertreatment.

2.7 Defining Opioid Stigma

Stigma has been extensively studied and theorized following the publication of Goffman's seminal text,[68] which defined stigma as "possessing and attribute which makes (someone) different from others" and "of a less desirable kind". Since then, a variety of academic and colloquial meanings have been attached to the concept. For the remainder of this review, we will refer to stigma as existing when (1) "people distinguish and label human differences", (2) "dominant cultural beliefs link labeled persons to undesirable characteristics", and (3) "labelled persons are placed in distinct categories so as to accomplish some degree of separation of 'us' from 'them.'[69] Extensive literature has demonstrated that stigma follows social structures including race, socioeconomic status, and gender, and can contribute to inequities in health.[70] In healthcare settings, stigmatization can negatively impact patients' self-perception, social support, and willingness to seek services, and these effects may be heightened by further stigmatizing behaviour of healthcare professionals.[71] Stigma may be categorized as either public stigma or self-stigma, and it has been shown the development of self-stigma follows the establishment of public stigma.[72,73]

In relation to opioids, it has been argued that the stigmatized history of opioids has defined the current epidemic, rather than arising as a parallel process in response to the crisis.[74] Regardless of the nature of the causal relationship between the modern opioid crisis and opioid stigma, it is clear that both medical and non-medical opioid use are affected by dimensions of stigma in public, clinical, and internalized domains.[75] Opioid stigma may be experienced from external sources, including media, peers, or healthcare providers, as well as internally, relating to patients' own feelings of fear or shame.

2.8 Public Stigma and Opioid Use

Over the past 20 years, news media coverage on the opioid epidemic and prescription opioids has dramatically increased, with more than 35,000 online news reports from 2018 to 2019 in the United States alone.[76] News stories discussing the opioid epidemic have been found to be far more likely to include stigmatizing terms, such as addict, compared to less stigmatizing alternatives, such as substance use disorder.[77] Public attitudes towards individuals with opioid use disorders have been found to have high levels of stigma, even among individuals with personal experiences relevant to opioid use.[78] The highly publicized and stigmatized presentation of the opioid crisis has resulted in high levels of stigma within the public consciousness, and these perceptions have permeated the oncology setting,[75] creating an environment which encourages of the formation of self-stigma among patients with cancer.

2.9 Discussion: Opioid Stigma in Cancer Settings

2.9.1 Pharmacovigilance & Indications of Opioid Stigma among Healthcare Professionals

The WHO identifies pharmacovigilance as aiming "to enhance patient care and patient safety in relation to the use of medicines, and to support public health programs by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines."[79] This concept is essential for safe and effective prescribing practices, including the prescribing of opioids for cancer pain management. However, disproportionate focus on the risks related to certain pharmaceuticals can lead to misuse of a benefit-to-harm framework, and thereby cause reluctance to enact optimal prescribing practices. The wide-reaching nature of the opioid epidemic may mean that both prescribers and patients are more likely to have personal experiences with opioid misuse or addiction, in addition to extensive press coverage, which may impact ideas about the utility of and risks associated with opioid use. These perceptions may not be consciously recognized by physicians and may lead to unintended consequences such as limited access to opioids, even among patients with advanced disease who are recognized to be in great need of these medicines.

Healthcare professionals often have very differing views on the role of opioids in cancer pain management, which may be related to their discipline and the type of care they provide.[80] For example, palliative care physicians may have very different perceptions of the dosage level and duration of prescription that is appropriate for patients, when compared to surgeons who typically prescribe opioids for acute post-operative pain.[80,81]

There are several studies which evaluate the diverse physician perceptions of opioid use in the context of cancer pain management. In a survey of more than 600 U.S. medical oncologists, a majority of respondents described themselves as less conservative in prescribing opioids than their peers and reported physician reluctance in opioid prescribing as a barrier to optimal pain management.[82] Despite reports indicating relatively high confidence among oncologists, it has been shown that physicians most satisfied with their abilities to manage CRP were actually the most reluctant in their use of strong opioids.[83] In another study, 41% of radiotherapists reported staff reluctance to prescribe opioids as a barrier to pain management.[84] Nearly a third of Eastern Cooperative Oncology Group physicians endorsed waiting until patient prognosis was 6 months or less before starting maximal analgesia,[85] and a survey of general healthcare providers found that more than 70% of respondents had concerns about NMOU in patients with cancer.[86] In a review of physician-related barriers to cancer pain management, findings indicated that physician reports consistently included concerns about high doses and side effects of opioids.[87] Each of these attitudes may represent a manifestation of opioid stigma and may act as contributor to pain undertreatment by adversely impacting pain management outcomes for patients with cancer. These studies demonstrate that it is common for healthcare professionals to endorse their own behaviours regarding cancer pain management, but reports are commonly critical towards peers, and hesitancy in opioid prescribing is commonly identified as a barrier to optimal pain management. While acknowledgement of the risks of opioid use is important for the essential practice of pharmacovigilance, in light of persistent issues of pain undertreatment in cancer populations, the question needs to be raised as to whether this vigilance has become over-rigorous due to increased stigmatization of opioid use.

While the adverse effects of the opioid epidemic are most prevalent in North America,[88] manifestations of opioid stigma have been observed globally. Among physicians managing cancer pain across 10 Asian countries, excessive regulation and patient fears of addiction were identified as key barriers to opioid prescribing and pain management.[89] In a survey of physicians in Cyprus, 70% of respondents identified opiophobia as a barrier to the appropriate management of cancer-related pain.[90] Strict regulation on opioid use was identified as a barrier in Palestine and Qatar,[91,92] and, similarly, across Europe excessive regulatory barriers in the accessibility of opioids have been identified,[93] which may negatively impact the management of cancer pain.

Dimensions of opioid stigma expressed by healthcare professionals are further affected by patient demographics, which may result in differential pain management that is prejudiced against minority or disadvantaged groups. Studies suggest that healthcare providers' distinction between patients who have legitimate or illegitimate pain tends to be influenced by class and racial characteristics,[94,95] similar to the delineation of stigma within these groups. Qualitative accounts have also demonstrated that healthcare providers are perceived to have personal biases related to the risks and benefits of long-term opioid therapy that are shaped by personal experiences and patient characteristics, including race and housing status.[80] Race and insurance type have both been found to be independently associated with the type of opioid prescribed to cancer outpatients,[96] and there is strong evidence of racial disparities in pain burden and management in cancer settings.[97] Stigma is inextricably related to these health disparities, as minorities and economically disadvantaged groups are easily stereotyped and assigned undesirable characteristics that are distanced from the "us" group. For example, Indigenous peoples may experience elevated external stigma due to an increased prevalence of substance use disorders, and there is significant discrimination against Indigenous peoples in healthcare settings.[98] This stigma has been shown to influence healthcare delivery and may lead to disparities in opioid prescribing and adequate pain treatment.[99]

In addition to evidence related to physician accounts, patients with advanced cancer report that their opioid use is stigmatized by healthcare providers, particularly those outside the oncology setting.[100] Patients with cancer commonly experience difficulties in filling opioid prescriptions caused by the pharmacy or pharmacist,[84] and report not only increased regulatory obstacles for filling opioid prescriptions, but also increased scrutiny from pharmacy staff that is perceived as judgmental and humiliating.[101,102] Oncologists have described logistical issues with prescribing opioids, including increased oversight and decreased comfort in prescribing, due to restrictive non-cancer regulations that impact their practice.[103]

In contrast to issues accessing opioids, patients have reported deferring pain management decisions to oncology providers who have advised them to take opioids.[63] Similarly, patients have reported feeling that oncology clinicians are quick to prescribe opioids without providing sufficient information.[104] These barriers in patient-provider communication and education can

lead to patients feeling that they have to self-manage their pain, and this self-management is commonly guided by personal stigma-related perceptions surrounding opioids.

2.9.2 Self-Stigma: Patients' Experience with Internalized Stigma and Opioid Use

Poor opioid adherence has been reported among patients with cancer, and research has found consistent underutilization of opioids by patients with cancer pain.[105,106] A study comparing longitudinal barriers to cancer pain management found that 40% of patients reported inadequate use of analgesics, and this high rate of inadequate management has been a consistent issue for the past 20 years.[107] This study additionally found that patient concerns about the risks of opioids have increased over this period. In a study of Taiwanese patients with cancer, negative beliefs regarding opioids were found to be significantly associated with poor analgesic adherence.[108] Stigma is one of the most significant patient-identified barriers to adequately managing pain, manifesting as internalized feelings of fear, shame, and discrimination based on their use of opioid analgesics.[100,107] These patient beliefs have been identified as a significant factor in choices related to analgesic use, which are generally modified toward lower dosage levels that fail to control pain.[100,102,109]

Fear is one of the most commonly reported feelings relating to opioid use among patients with advanced cancer, and may arise from concerns regarding addiction, dependence, diminishing opioid efficacy, and side effects.[100,102,104,109–112] Concerns of addiction were found to be among the greatest patient-perceived barriers to cancer pain management in a review of both Western and Asian cancer patients.[113] The opioid epidemic has been identified as foundational to patients' beliefs regarding the use of opioids, and media or news coverage are contributors to patient fears.[102] Patients commonly view opioid use as an ethical issue and see taking pain medication as "caving in."[102] Patients may attempt to gain control over their addiction fears through opioid-restricting behaviours, including dose reductions or avoidance of long-acting or strong opioids.[102,104,110] Another recurring contributor to fear includes the belief that proactive or earlier use of opioids would result in inability to achieve relief from pain "when they really need it,"[110] demonstrating worries relating to the development of tolerance. Patients also expressed that they avoided taking opioids for fear that dependency would develop, and that opioid use would become daily or routine.[110,114] Strong opioids were largely viewed as a "last resort", and

patients reported opioid-avoidant behaviours until pain became totally unbearable or required hospitalization.[102,112]

Beyond fears regarding the risk of opioid use, patients often feel shame or guilt, which are constructs of the stigma surrounding opioid use. While it may be viewed as rational that patients have concerns about opioid dependency or side effects, feelings of shame and guilt, especially among patients who are following medical instruction and gaining clinical benefit from opioids, are largely detrimental. Even when partaking in opioid-restricting behaviours, patients express feeling morally compromised and experiencing guilt relating to substance use.[102] It was common for patients to draw false equivalencies to other behaviours, such as smoking, drinking, or other drugs,[102,111] and these comparisons contribute to increasing feelings of shame. Patients commonly used highly sensationalized terms, such as addict and junkie,[100,102,110] which reflect their internalized stigma against individuals with opioid use disorders. The public perception of opioids as "bad", and the idea that people who take opioids are also "bad", is pervasive among patients with advanced cancer and extends to their ability to perceive themselves as good people who deserve relief from pain.[100,102] The shame experienced by these patients is a direct result of opioid-related stigma and impacts not only patients' ability to manage their pain, but also their psychological wellbeing and self-regard.

A final major theme identified from studies investigating self-stigma among patients with advanced cancer is discomfort with sharing concerns with providers, and feelings that they will be perceived as a "pill-seeker."[102] Patients reported avoiding conversations with their healthcare providers, for fear of being judged or undergoing scrutiny regarding the legitimacy of their pain and need for opioids.[102] In the alternate case, patients displayed avoidant behaviours to healthcare professionals who were encouraging opioid use, feeling uncomfortable with sharing concerns about addiction and/or related noncompliance with prescription instructions.[104,114] In either case, the effective communication between patient and provider was compromised, and ability to engage in productive conversations, including implementing a benefit-to-harm framework for shared-decision making, were inhibited.

2.9.3 Future Directions

Attempts to destigmatize patient perceptions of opioids can remove a barrier from the effective management of pain and allow patients to feel more comfortable with adequately

managing their pain. While there is a growing interest in investigating the manifestations of opioid stigma in this population, there is a general lack of evidence on how these issues may be combatted. Additionally, the majority of research on patient experiences of opioid stigma has been conducted in the United States, and more research would be useful to better understand global patient experiences.

Further education on these topics is needed among clinicians who, as a result, may be better able to communicate with patients in a destigmatizing manner. A conceptual framework for opioid stigma has been developed for the context of cancer pain[75] and may be beneficial in designing interventions to address this barrier to pain management. The opioid stigma framework (OSF) is useful for designing health system interventions which may be targeted to specific domains, including intersecting stigmas, manifestations of stigma, and the impacts of opioid stigma for patients.[75] Further research is warranted to design interventions which address the underlying mechanisms of opioid stigma using this framework.

In other stigmatized domains, such as mental health, tailored multilevel interventions to educate and communicate about stigma have been found to be beneficial in alleviating negative perceptions.[115] Studies which employ interventions to reduce the stigma related to substance use disorders may additionally be helpful in designing strategies for cancer populations.[116] Clinicians, pharmacists and other healthcare professionals in this area should be aware of the highly stigmatized nature of opioid use in this setting and attempt to communicate with patients in ways that destigmatize effective pain management.

In addition to interventions directly targeting the foundations and consequences of opioid stigma, the effective treatment of cancer-related pain requires involvement of a multidisciplinary team.[117] It has been shown that the provision of palliative care can help to reduce the stigma surrounding appropriate pain management for patients with cancer.[118] Continued efforts should be made to integrate palliative care specialists, psychological support, pharmacists, and other healthcare professionals into patient-centered oncology care. Furthermore, improving the availability of substance use disorder or addiction specialists may be particularly useful for providing effective pain management to patients with a history of substance use disorders.[119]

There is a need for personalized pain management strategies among patients with cancer, for whom both their pain and ability to manage it are modulated by individual factors such as

mood, beliefs, culture, and pain etiology. Guidelines have been developed which encourage open conversations about patient goals and concerns regarding pain management which can facilitate personalized treatment decisions with the help of a multidisciplinary team.[22] However, these guidelines require targeted interventions to aid their successful implementation in routine cancer care. The integration of palliative, supportive, and oncology care may allow for cancer-related pain to be better assessed and addressed, as well as facilitate improved communication between patients and their team of healthcare professionals.

Additionally, the use of multimodal pain management strategies may aid in addressing pain undertreatment and the outcomes resulting from opioid stigma. The use of atypical opioid analgesics[120] or further research into non-opioid analgesia may be useful for improving pain management in these settings.[121] Furthermore, there is a growing body evidence for non-pharmacological management of cancer-related pain, including a variety of psychosocial interventions for patients with cancer,[122,123] which provide additional evidence for the importance of multidisciplinary involvement in cancer management.

2.10 Conclusions

Opioids are an essential therapeutic option for pain and symptom management among patients with advanced cancer. However, the opioid crisis has led to highly publicized and widespread stigmatization of opioid use, which affects both patients and healthcare providers. While responses to the opioid crisis were not intended to affect the cancer population, stigma has transcended the intended scope of guidelines and become a significant barrier to pain management for patients with advanced cancer. Stigmatization manifests among healthcare professionals who provide access to opioids and can result in disparities in access to resources among minorities or groups with increased stigma.

In spite of healthcare professionals being the gatekeepers of opioid analgesics, the most significant barriers to cancer pain management relate to the self-stigma experienced by patients. Patients with advanced cancer have fears related to addiction and diminishing returns, shame regarding their need for opioids, and difficulties communicating with providers about these topics. Self-stigma can act as a barrier to pain reporting, which makes physicians' pain assessment impossible. This stigma may also act as a barrier to prescription adherence, which

means that, even in the case of perfect prescribing practices, patients may not experience freedom from their pain.

Healthcare professionals should therefore be prepared to initiate and maintain conversations with patients such that stigma is reduced, not amplified or ignored. Specific and standardized risk assessment tools should take into account opioid stigma in order address imbalanced pharmacovigilance. Furthermore, accurate risk assessment for the advanced cancer population cannot be accomplished without a better understanding of the real-world risks of opioid use, which would allow for a well-informed benefit-to-harm framework for decision-making. More research is needed, not only to understand the experience of opioid stigma by these patients, but to provide complete information to patients, which demonstrates that they do not need to be afraid, shameful, and living with uncontrolled pain.

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CHAPTER 3: LONG-TERM OPIOID PRESCRIBING AND RELATED HOSPITALIZATIONS OR EMERGENCY DEPARTMENT VISITS AMONG PATIENTS WITH METASTATIC CANCER

Bridging Text

Given the findings of the literature review, it is clear that patients with metastatic disease are in need of safe and effective opioid prescribing. However, the review highlighted current knowledge gaps, including the lack of sufficient evidence regarding the real-world risks of opioid use in this context. Therefore, the following chapter aims to use population-based data to investigate the number of patients receiving long-term opioid prescribing and experiencing associated opioid-related healthcare encounters. These findings will be useful to address the outlined patient-identified concerns and inform a benefit-to-harm framework of opioid prescribing for patients living with chronic metastatic disease.

3.1 Abstract

***Background**:* Although opioids are effective for cancer pain management, long-term use may result in adverse effects which are understudied among patients with metastatic disease.
Objectives: To describe long-term opioid prescribing among patients with metastatic cancer and investigate how long-term prescribing practices are associated with the incidence of opioid-related hospitalizations and emergency department visits.
***Methods**:* This retrospective cohort study included all patients diagnosed with stage IV cancer in Alberta, Canada from 2004-2017 who had ≥1-year of follow-up and were opioid naïve at diagnosis. Patients were identified from and followed using linked administrative health data. Long-term prescribing was defined as receiving a ≥90-day supply of opioids with a <30-day gap in supply within a 180-day period. The incidence rate of opioid-related encounters was compared based on characteristics of long-term prescribing (timing, dosage, duration, and concurrent medications).
Results: The study included 10,927 patients, 2521 (23%) of whom received long-term opioid prescribing. These practices became more common as patients approached the end-of-life. Opioid-related hospitalizations and emergency department visits were experienced by 85 (3.4%) recipients of long-term prescribing. Higher dosage and concurrent prescribing of anxiolytics,

benzodiazepines, antidepressants, and neuroleptics were associated with a higher incidence of opioid-related encounters.

Conclusions: Long-term opioid prescribing is common and patients receiving high opioid dosage or psychoactive medications have an elevated risk of experiencing encounters related to overdose or opioid use disorders. Further research is needed to determine strategies to minimize opioid-related harms for these patients while providing appropriate pain and symptom management.

3.2 Key Statements

i) What is already known about the topic?

- Treatment options for metastatic cancer are improving, meaning that metastatic cancer is commonly experienced as a chronic incurable disease.
- Opioid use is common among patients with metastatic disease, who experience high levels of pain and often require palliative care.

ii) What this paper adds

- Long-term opioid use is a relevant issue for patients living with chronic metastatic cancer, although it is primarily used near the end-of-life.
- Patients receiving high dose long-term opioid prescribing and concurrent psychoactive medications were more likely to experience opioid overdose or opioid use disorders which led to healthcare utilization.

iii) Implications for practice theory, or policy

- Patients self-managing opioids near the end-of-life may benefit from additional guidance on safe opioid use considering high levels of psychoactive drug use and declining health status, which may increase the risk of toxicity and overdose.

3.3 Introduction

Cancer is the leading cause of death in Canada and presentation with metastatic disease is common, with more than 10,000 Canadians diagnosed each year.[1] Advances in treatment have allowed survival times for patients with metastatic disease to significantly increase.[2] For example, the 2-year survival rate for patients with metastatic non-small-cell lung cancer has increased nearly five-fold since the 1970s,[3] and for patients with metastatic breast or prostate cancer the three-year survival rate is nearing 50%.[4] As a result, increasing numbers of patients experience metastatic cancer as a chronic disease, defined by the Centers for Disease Control and Prevention as conditions lasting for 1 year or more.[5] Despite the large number of impacted individuals and their increased survival time, issues related to metastatic survivorship remain understudied.[4,6]

Due to advanced disease and incurable diagnoses, these patients often face significant psychological and physical challenges and receive care focused on pain and symptom management. A majority of patients experience cancer pain, with an estimated prevalence of 66% among patients with metastatic cancer.[7] Opioids are recommended for the treatment of this pain and have been found to be highly effective for cancer pain management.[8] However, opioid use can result in adverse effects and its role in managing chronic pain is debated.[9] Long-term use may lead to reduced efficacy with the possibility of developing toxicities, dependence, or misuse.[9] Despite these concerns, long-term use is common within cancer populations, estimated to impact 14% of patients with cancer and an even higher proportion among those with advanced disease.[10] Furthermore, patients with metastatic disease are often prescribed high dose opioids and may be susceptible to overdoses or aberrant use behaviors which can lead to emergency department (ED) visits, hospitalizations, or even death.[11] While there are a limited number of studies investigating opioid-related hospitalizations and ED visits among patients with cancer,[11–14] there is currently no information specific to patients with metastatic disease.

The benefit-to-risk profile of opioid use is highly complex as it varies by individual, as well as over time. As patients enter the end-of life phase of disease, concerns regarding chronic adverse effects may be de-prioritized due to benefits experienced over a shortened prognosis time.[15] However, considering the changing landscape wherein metastatic survivorship may continue for years, it has become increasingly important to investigate long-term opioid use and

consider the potential for associated adverse effects in this population.[16] This study therefore aimed to identify patients receiving long-term opioid prescribing following a diagnosis of metastatic cancer and investigate how differing long-term prescribing practices relate to the incidence of opioid-related ED visits and hospitalizations.

3.4 Methods

3.4.1 Data Sources

Our study used retrospective data from the province of Alberta, Canada, including the Alberta Cancer Registry (ACR), Pharmaceutical Information Network (PIN), Discharge Abstract Database (DAD), and National Ambulatory Care Reporting System (NACRS). The study population was identified from the ACR, and personal health number was used to link datasets. The ACR records population-based data on cancer patients in the province and maintains the highest certification from the North American Association of Central Cancer Registries. The province of Alberta serves over 4 million citizens with more than 20,000 cancer patients diagnosed annually.[17] The PIN records data on all prescriptions filled at outpatient pharmacies across the province. The DAD and NACRS record data on all patients discharged from hospital and from ambulatory care visits, respectively.

3.4.2 Study Population

The study included patients diagnosed with a stage IV solid cancer *(Table A1.1)* from 2004-2017. This study period was selected to allow for adequate time to ascertain prescribing patterns and outcomes. Patients were excluded if they died within 1-year of diagnosis, or if their follow-up time was <1-year between diagnosis and the date of data pull. A timeframe of 1-year was selected based on definitions of chronic disease[5] and end-of-life care.[18] Patients were excluded if they were not opioid-naïve at diagnosis, i.e., had filled opioid prescriptions in the 12 months to 31 days preceding diagnosis,[19] or had a previously documented opioid use disorder. Included patients were followed from diagnosis until the date of data pull (July 2019) or until death, whichever occurred first.

3.4.3 Long-Term Opioid Prescribing

Long-term opioid prescribing was defined as receipt of a 90-day or greater supply of opioids with less than a 30-day gap in supply within a 180-day period following diagnosis.[20] Opioid prescriptions were identified from the PIN database using Anatomical Therapeutic Chemical (ATC) code and considered active for the number of days prescribed beginning at the date of dispensing to the patient. Oral morphine equivalent daily dose (MEDD) was estimated using the prescribed amount specified in PIN data and calculated using equianalgesic dose conversions *(Table A1.2)*.[21,22] Prescribing practices were characterized in terms of duration and dosage, with categories defined by median duration in the study population and mean MEDD >100mg, respectively. Among decedents, the timing of opioid prescribing was characterized relative to death; early long-term prescribing was defined as initiation prior to the end-of-life phase (i.e., last year of life).[18] Concurrent prescriptions received during long-term prescribing were identified from PIN data and categorized according to ATC-code *(Table A1.3)*.

3.4.4 Patient Characteristics

Patient characteristics included in the analysis were selected based on previous literature investigating long-term opioid use and related healthcare utilization and included age, sex, cancer type, and treatment type.[11,14,19,23] Mental health and substance use diagnoses were identified by searching diagnostic codes from patient healthcare encounters in the 3-years preceding diagnosis *(Table A1.4)*.[24] Socioeconomic status was accounted for using neighborhood-level household income (in Canadian dollars) and educational attainment (in percentage completing high school) based on patient postal code and categorized using census benchmarks.

3.4.5 Opioid-Related Encounters

Opioid-related encounters were defined as hospitalizations or ED visits relating to opioid overdose or opioid use disorder, as defined in previous literature.[14,24,25] Encounters occurring after initiation of long-term prescribing were identified from DAD and NACRS using International Classification of Diseases, 10th edition, (ICD-10) codes T40.0-4, T40.6 & X42 for opioid overdose/poisoning and F11.x for opioid use disorders. If an ED visit resulted in hospital admission, this was considered as a single encounter.

3.4.6 Statistical Analysis

Patient characteristics were described using median [interquartile range (IQR)] or frequency (%). Continuous variables were compared using t-tests and categorical variables were compared using χ^2 tests to assess differences between recipients of long-term prescribing, compared to patients who did not receive long-term prescribing. Multivariable logistic regression was used to investigate characteristics associated with receipt of long-term prescribing, as well as characteristics associated with early long-term prescribing. Subgroup analyses were carried out by sex, as well as for common cancer types. Sensitivity analyses were conducted for an alternate definition of long-term prescribing, which included patients who received ≥10 opioid prescriptions within a 1-year period.[128] The incidence rate of opioid-related encounters was calculated as the total number of hospitalizations and ED visits divided by person-years of follow up after initiation of long-term prescribing. Incidence rates were presented with Poisson 95% confidence intervals (CI) and compared using p-values for the incidence rate ratio (IRR). Sensitivity analyses were conducted for the definition of early onset, as well as categorizations of duration (ranging from cut-off of 6-months to 2-years) and dosage (ranging from cut-off of 50mg to 200mg mean MEDD). Statistical significance was defined using an alpha level of 0.05. Analyses were carried out using R version 4.3.2 (2023).

3.5 Results

3.5.1 Patient Characteristics and their Association with Long-Term Prescribing

The study included 10,927 patients with stage IV cancer who were opioid-naïve at diagnosis and had a follow-up time ≥1-year *(Figure 3.1).* The median follow-up time of included patients was 28 months (IQR 18, 49). Patients had median age of 64 years old, 60% were male, and the most common primary tumor sites were colorectal (20%), lung (20%), and prostate (18%) *(Table 3.1)*.

Among these patients, 2521 (23%) received long-term prescribing after diagnosis. When using an alternate definition, including receipt of ≥10 opioid prescriptions within 1-year, 2850 patients (26%) were found to be long-term prescribing recipients *(Table A1.5)*. Compared to patients who did not receive long-term prescribing, recipients were younger, were less likely to have surgical treatment, and were more likely to be deceased, to have bone metastases, and to have a history of mental health diagnoses (*Table 3.1)*. These results were consistent after

adjusting for covariates (*Table A1.6)* and when using the alternate definition of long-term prescribing *(Table A1.7).*

3.5.2 Characteristics of Long-Term Opioid Prescribing Practices

The duration of long-term prescribing ranged from 90 days to 4216 days (11.55 years) with a median of 257 days (IQR 156, 461) *(Figure 3.2a).* Over the course of long-term prescribing, MEDD increased from a mean starting dose of 71.0 mg (SD: 128.9mg) to a final dose of 167.8 mg (SD: 296.4mg) *(Figure 3.2b).* The increase was statically significant ($p<0.001$) and greater among patients with a ≥180-day prescribing period *(Table A1.8)*.

Among decedents (n=2091), the median time from initiation of long-term prescribing to death was 348 days *(Figure 3.2c).* Long-term prescribing became more common as patients approached death *(Figure 3.2d),* with 53% of decedents having these prescribing practices initiated within the last year of life, and 22% within the last 6-months of life. From multivariable logistic regression, patients with younger age, longer survival time, no surgical treatment, and bone metastases had a significantly higher odds of receiving early long-term prescribing (*Table A1.9)*. The odds of receiving early long-term prescribing were 1.72 times greater (95% CI: 1.33, 2.22) among patients with, compared to patients without, bone metastases. In subgroup analyses, younger age was associated with early long-term prescribing among males, but not females *(Table A1.10)*.

3.5.3 Incidence of Opioid-Related Hospitalizations and Emergency Department Visits

Following initiation of long-term prescribing, 85 patients (3.37%) experienced an opioid-related encounter. There were 101 opioid-related encounters, resulting in an incidence rate of 2.36 (95% CI 1.92, 2.86) encounters per 100 person-years of follow-up. 52 events were coded as relating to opioid overdose/poisoning and 49 events were coded as relating to opioid use disorders *(Table 3.2)*. Most encounters occurred in the end-of-life phase, with 67 occurring in patients' last year of life and 35 occurring within 90-days of death *(Table 3.2)*. There were no fatal overdose events; of the 9 encounters resulting in inpatient mortality, none attributed opioid overdose as the cause of death.

3.5.4 Association of Prescribing Practices with Opioid-Related Encounters

From univariate analyses, patients who experienced an opioid-related encounter were more likely to have high opioid dosage, longer duration of prescribing, and early long-term prescribing, compared to patients who did not experience an opioid-related encounter *(Table A1.11)*. After adjusting for follow-up time and comparing incidence rates, there was no association between the duration of prescribing and opioid-related encounters (p=0.65) *(Figure 3.3)*. This finding was consistent when tested in sensitivity analyses for comparing various categorizations of prescribing period *(Table A1.12)*. Additionally, after adjusting for follow-up time, the incidence of opioid-related encounters was found to be lower among patients who had early long-term prescribing (2.79 vs. 4.98 encounters per 100 person-years). High dosage (mean MEDD >100mg), as well as concurrent prescribing of anxiolytics, benzodiazepines, antidepressants, and neuroleptic medications were significantly associated with an higher incidence of opioid-related encounters *(Figure 3.3)*. These findings were consistent in sensitivity analyses testing various categorizations of high dosage level and the incidence rate was found to progressively increase with increasing dosage *(Table A1.12)*.

3.6 Discussion

Our study used population-based data to investigate long-term opioid prescribing practices among patients living with metastatic cancer as a chronic disease. We found that nearly 1-in-4 patients were recipients of long-term prescribing following diagnosis and 3.4% of recipients experienced an opioid-related hospitalization or ED visit. The rate of long-term opioid prescribing found in this study is higher than rates reported among opioid-naïve patients following curative-intent treatment, which range from 2 to 18%.[19,27-29] The higher prevalence of these prescribing practices is likely attributable to increasing opioid use to address increasing symptom burden as patients with metastatic cancer approach the end of their lives.[30]

Recipients of long-term opioid prescribing were a distinct population with significant differences in clinical and demographic characteristics compared to patients without long-term prescribing. Notably, recipients of long-term prescribing were more likely to have a history of mental health diagnoses, consistent with findings among cancer survivors[23] and non-cancer populations.[31] This may be a useful consideration when assessing potential risks of opioid prescribing in this population, as the association with mental health conditions, such as

depression, has been postulated to relate to the use of opioids for treating nonphysical pain/suffering, as well as possible deficits in endogenous opioid function.[31,32] Furthermore, depression has been shown to be associated with an increased risk of nonmedical use of opioids which may relate to a greater risk of overdose and development of opioid use disorders.[33,34] These findings indicate that mental health history may be a shared risk factor for long-term opioid prescribing between patients with chronic metastatic cancer and patients with other chronic pain conditions. As such, consistent screening for mental health concerns among patients with metastatic cancer receiving opioids may be useful to encourage the provision of psychosocial support and increased monitoring for chemical coping with opioids.[32,34]

Despite long-term prescribing impacting a relatively large proportion of patients in our study, our findings indicate that it was primarily employed during the end-of-life phase of disease. As patients approach death, they often face disease progression, functional impairments, and troubling symptoms such as poorly controlled pain. Within this phase, opioid prescribing is likely initiated to address these changes, which necessitate increased pain and symptom management. These findings are in agreement with previous research showing that opioid prescribing tends to increase near the end-of-life.[35] Among patients with early long-term prescribing, bone metastasis were more common, which can cause severe pain, pathologic fractures, and/or spinal compression.[36] Additionally, receipt of surgical treatment was less common, which may be an indicator of patients with less active care goals and an increased desire for or openness to palliative care. Taken together, these findings may demonstrate that long-term opioid prescribing practices are largely used appropriately in this setting, in that they are related to clinical factors associated with increased pain, indicators of differing patient priorities, or are initiated near end-of-life, when patients often face increased symptom burden.

Although opioid prescribing is important for helping maintain patient quality of life, particularly near end-of-life,[30] recipients of long-term prescribing were found to be at a relatively high risk of experiencing opioid-induced adverse effects leading to hospitalization or ED visits. Opioid-related encounters were experienced by 3.4% of long-term prescribing recipients in our study, with 1.9% experiencing an encounter related to opioid overdose/poisoning. While this is the first study specifically investigating this outcome for patients with metastatic cancer, our results may be compared to a study by Merlin et al., which reported only 0.1% of long-term prescribing recipients with cancer experiencing an overdose event.[13] The increased risk of

overdose observed in our study is likely related to more advanced disease, as Merlin et al. included patients regardless of stage and reported <6% of patients dying in the 90-day period following overdose, compared to 35% in this study.[13] An increased risk of overdose near end-of-life may additionally explain the negative association between opioid-related encounters and early long-term prescribing, as patients outside the end-of-life phase are less likely to experience opioid-related encounters. As cancer progresses, patients increasingly experience issues like delirium, sepsis, and organ dysfunction which may increase their susceptibility to overdose.[37] Therefore our findings indicate that patients self-managing opioids near end-of-life may benefit from increased education on safe opioid use and greater monitoring for signs of toxicity to address their relatively high risk of overdose.

In line with previous literature,[25] the incidence of opioid-related encounters was found to increase with higher dosage, and dosage increased over the course of long-term prescribing. While this may indicate the development of opioid tolerance among patients receiving long-term prescribing, it is likely that these changes are also driven by disease progression leading to increased pain. Further investigations accounting for patient-reported outcomes and disease progression may be useful to explain the observed increase in opioid dosage during long-term prescribing.

In addition to dosage level, the incidence of opioid-related encounters was greater among patients receiving psychoactive prescription drugs, potentially implicating polypharmacy and drug-drug interactions in the incidence of these events. Polypharmacy is extremely prevalent among advanced cancer patients near end-of-life, with one study reporting a prevalence of 95%.[38] The contribution of polypharmacy to overdose events and healthcare utilization in this setting requires further investigation. Due to the higher incidence of healthcare encounters related to overdose and opioid use disorders, patients receiving high dosage and concurrent psychoactive medications may benefit from increased education on and monitoring for opioid-related adverse effects. Additionally, studies investigating interventions to mitigate the risk of opioid-related encounters are warranted and should consider implementation of multimodal management strategies, which may be effective in reducing patient pain, as well as comorbidities related to psychoactive drug use, such as anxiety and depression.[32]

3.6.1 Limitations

This study is unable to determine if identified associations represent causal relationships. Due to the population-based design, our study should have good generalizability; however prescribing practices may vary based on regional regulations and prescriber attitudes. Additionally, the use of population-based data means that our study was only able to follow patients up until July 2019, and generalizability to current patients may be limited, especially given the COVID-19 pandemic which occurred after this timeframe. Furthermore, our study did not formally investigate changes in prescribing patterns over time.

Our findings are limited to prescriptions filled at outpatient pharmacies; the lack of inpatient data may explain the observed decline in long-term prescribing immediately preceding death *(Figure 3.2d)*. However, inpatient use of opioids is less likely to be inappropriate due to increased oversight from clinical staff. We were additionally unable to determine patient adherence with prescription instructions. While poor adherence has been reported, it has been found to tend towards opioid-restricting behaviours,[39] which should have limited impact on our findings as long-term prescribing primarily identifies patients filling multiple prescriptions over an extended period. Additionally, identification of opioid-related encounters was dependent on diagnostic coding in administrative data and may be subject to misclassification errors; this would likely lead to an underestimation of the rate of opioid-related encounters.[40] Furthermore, our study did not account for patient-reported outcomes or goals of care, which may impact decision-making surrounding opioid use. Further investigation is needed to better understand the relationship between long-term prescribing, pain severity, and treatment priorities.

3.7 Conclusions

Long-term opioid prescribing is relatively common among patients living with chronic metastatic cancer and is primarily utilized during the end-of-life phase of disease. Recipients of long-term prescribing are at risk of experiencing opioid overdose or use disorders which result in hospitalization or ED visits, particularly as they near the end-of-life. These encounters were additionally more common among patients receiving higher opioid dosage and psychoactive medications. Efforts to improve opioid safety for these patients, such as increased education and monitoring from healthcare providers, may be beneficial. Further research is needed to understand the causal factors related to these adverse effects, as well as determine ideal

prescribing practices to minimize their incidence while providing appropriate care to address patients' pain and symptom management needs.

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Ethics Statement:

This study was approved by the Health Research Ethics Board of Alberta (HREBA.CC-23-0270).

Conflict of Interest:

The authors have no potential conflicts of interest to declare with respect to the research, authorship, or publication of this article.

Tables and Figures:

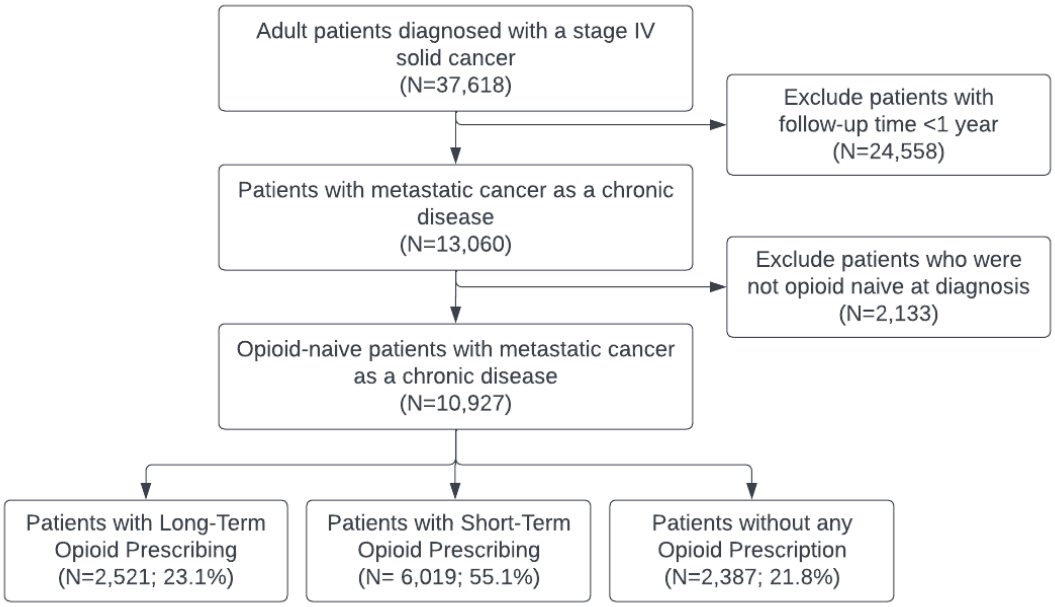

Figure 3.1: Flow Diagram of Cohort Selection and Opioid Prescribing Subgroups

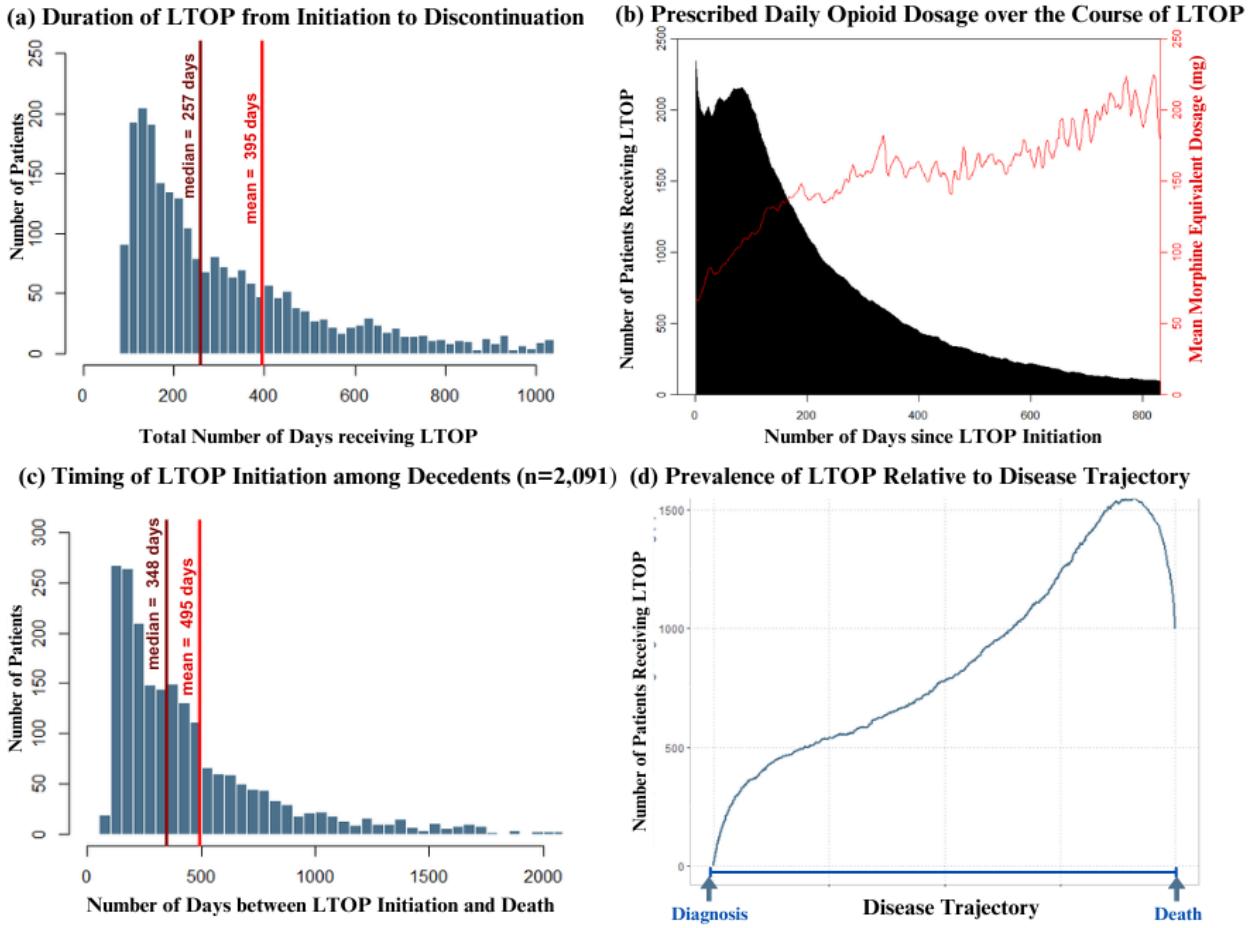

Figure 3.2: Characteristics of Long-Term Opioid Prescribing (LTOP) Practices

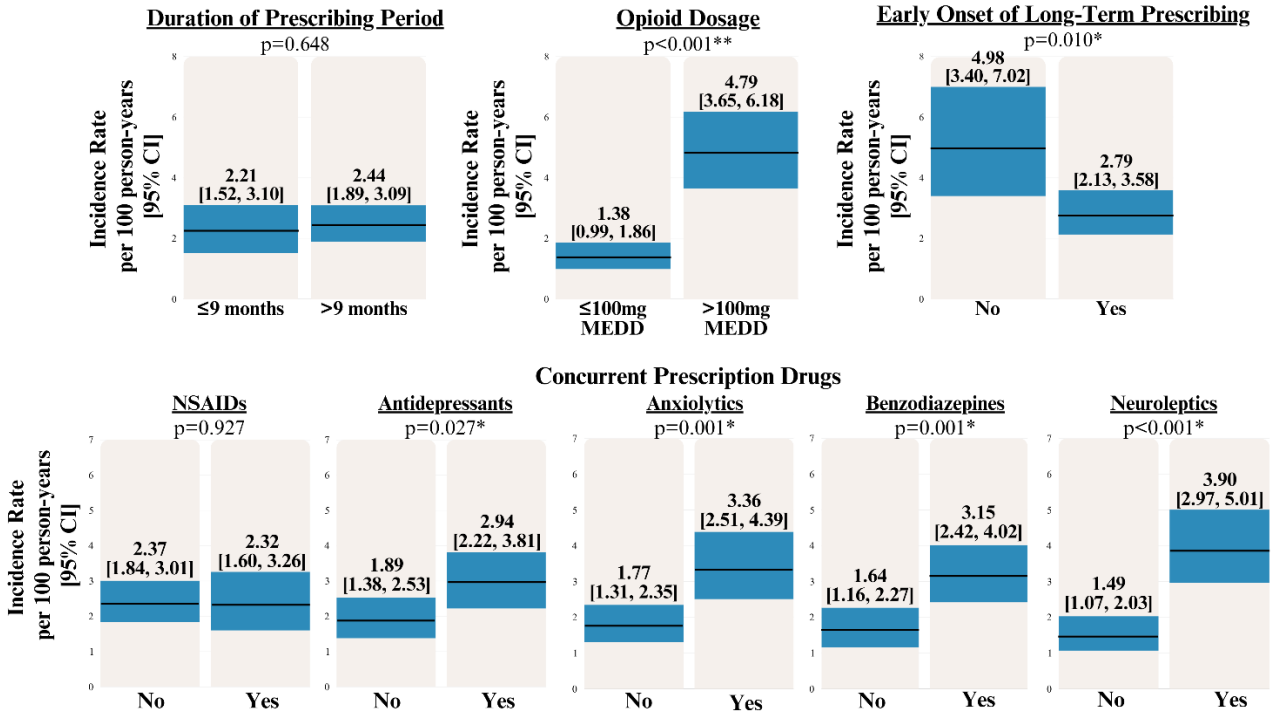

Figure 3.3: Association of Long-Term Prescribing Characteristics with the Incidence of Opioid-Related Encounters

Table 3.1: Patient Demographic & Clinical Characteristics and their Association with Long-Term Prescribing

	Total Cohort	Recipients of long-term opioid prescribing	Patients without long-term opioid prescribing	p-value
N	**10,927**	**2,521 (23.07%)**	**8,406 (76.93%)**	
Age at Diagnosis	64.01 ± 12.70	61.93 ± 11.98	64.62 ± 12.85	<0.001*
Vital Status[1]				<0.001*
Alive	3,314 (30.33%)	430 (17.06%)	2,884 (65.69%)	
Deceased	7,613 (69.67%)	2,091 (82.94%)	5,522 (34.31%)	
***Survival Time** (days) (among decedents)*	*948.59 ± 685.75*	*1039.64 ± 733.91*	*914.11 ± 663.41*	*<0.001**
Sex				0.389
Male	6,582 (60.24%)	1,500 (59.50%)	5,082 (60.46%)	
Female	4,345 (39.76%)	1,021 (40.50%)	3,324 (39.54%)	
Area of Residence[2]				
Urban	8,251 (75.51%)	1,839 (72.98%)	6,412 (76.31%)	<0.001*
Rural	2,672 (24.45%)	681 (27.02%)	1,991 (23.69%)	
Tumor Group				
Colorectal	2,195 (20.09%)	481 (19.08%)	1,714 (20.39%)	
Lung	2,164 (19.80%)	540 (21.42%)	1,624 (19.32%)	
Prostate	2,007 (18.37%)	504 (19.99%)	1,503 (17.88%)	
Head & Neck	1,657 (15.16%)	380 (15.07%)	1,277 (15.19%)	<0.001*
Breast	949 (8.68%)	225 (8.93%)	724 (8.61%)	
Other	1,955 (17.89%)	391 (15.51%)	1,564 (18.61%)	
Presence of Bone Metastasis	2,785 (25.49%)	888 (35.22%)	1,897 (22.57%)	<0.001*
Treatment Received				
Chemotherapy	6,083 (55.67%)	1,410 (55.93%)	4,673 (55.59%)	0.764
Surgery	4,214 (38.57%)	812 (32.21%)	3,402 (40.47%)	<0.001*
Radiation	3,152 (28.85%)	741 (29.39%)	2,411 (28.68%)	0.489
Hormone Therapy	2,538 (24.65%)	658 (26.10%)	1,880 (22.36%)	<0.001*
Immunotherapy	462 (4.23%)	99 (3.93%)	363 (4.32%)	0.392
Year of Diagnosis				
2004-2008	3,140 (28.74%)	695 (27.57%)	2,445 (29.09%)	
2009-2013	4,097 (37.49%)	1,066 (42.28%)	3,031 (36.06%)	<0.001*
2014-2017	3,690 (33.77%)	760 (30.15%)	2,930 (34.86%)	
History of Mental Health Diagnoses[2]				
Substance Dependence	357 (3.27%)	115 (4.56%)	242 (2.88%)	<0.001*
Anxiety Disorders	899 (8.23%)	242 (9.60%)	657 (7.82%)	0.004*
Depressive Disorders	1,031 (9.44%)	329 (13.05%)	702 (8.35%)	<0.001*

[1]As of 2019/07/22

[2] Missing data for n=4

[3]See Appendix Table 1 for diagnostic codes used to identify history of mental health diagnoses from healthcare encounters in Alberta in the 3 years prior to diagnosis.

* Represents statistical significance given an alpha of 0.05

Table 3.2: Incidence of Opioid-Related Encounters among Long-Term Prescribing Recipients

	All Opioid Related Encounters		Encounters Relating to Opioid Overdose		Encounters Relating to Opioid Use Disorder	
	Number of Patients	***Number of Encounters***	*Number of Patients*[1]	*Number of Encounters*	*Number of Patients*[1]	*Number of Encounters*
N	***85***	***101***	*48*	*52*	*38*	*49*
Incidence among long-term recipients	**3.37 per 100 patients**	**2.36 per 100 person-years**	1.90 per 100 patients	1.21 per 100 person-years	1.51 per 100 patients	1.14 per 100 person-years
95% CI	2.74, 4.16	1.92, 2.86	1.44, 2.52	0.91, 1.59	1.10, 2.07	0.85, 1.51
Encounters Requiring Hospital Admission	68 (67.3%)		32 (61.5%)		37 (75.5%)	
Mean Length of Stay	*13.4 ± 16.0 days*		*12.1 ± 15.1 days*		*15.2 ± 17.0 days*	
Mean Time from Encounter to Death[2]	273.9 ± 292.8 days		221.7 ± 259.7 days		329.6 ± 317.8 days	
Number of Encounters[2]:						
In Last Year of Life	67 (66.3%)		38 (73.1%)		29 (59.2%)	
In Last 90-days of Life	35 (34.7%)		22 (42.3%)		13 (26.5%)	
In Last 30-days of Life	20 (19.8%)		12 (23.1%)		8 (16.3%)	
Resulting in Inpatient Mortality	9 (8.9%)		4 (7.7%)		5 (10.2%)	
Number of Encounters for Palliative Care[3]	34 (33.7%)		13 (25.0%)		21 (42.9%)	

[1] 1 patient experienced encounters coded as relating to both opioid overdose and opioid use disorder.
[2] Missing for n=8 encounters as patients were not deceased at the time of data pulling.
[3] Identified as any encounters with ICD-10 code Z51.5

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CHAPTER 4: THE CONTRIBUTION OF NONMEDICAL OPIOID USE TO HEALTHCARE ENCOUNTERS FOR OPIOID POSIONING AND USE DISORDERS AMONG LONG-TERM USERS WITH METASTATIC CANCER

Bridging Text

The previous chapter confirmed that patients with metastatic cancer who are receiving long-term opioid prescribing are at risk of experiencing opioid-related healthcare encounters. However, due to the retrospective, quantitative study design, we were unable to adequately assess the types of adverse effects being experienced by patients, as well as the factors contributing to their onset. Therefore, the following chapter aims to describe opioid-related healthcare encounters occurring among patients receiving long-term opioid prescribing and determine the number of patients thought to be engaging in nonmedical opioid use (NMOU) behaviours. This further serves to validate findings from the narrative review, by providing information related to manifestations of opioid stigma which impact patients' ability to manage their pain.

4.1 Abstract

Purpose: Opioid misuse is increasingly recognized as a relevant problem among patients with cancer. However, the applicability of these concerns for patients with metastatic disease is complicated by shorter prognoses and greater symptom burden. This study aimed to investigate whether nonmedical opioid use (NMOU) was identified as contributing to opioid-related healthcare encounters among patients with metastatic cancer receiving long-term prescribing.

Methods: Patients with stage IV cancer diagnosed from 2004-2017 who received long-term opioid prescribing and experienced ≥1 opioid-related encounter (emergency department visit or hospitalization related to opioid poisoning or opioid use disorder) were retrospectively identified using administrative health data from Alberta, Canada. Patient charts were reviewed to identify any documentation of NMOU behaviours. Patient characteristics were compared between those with and those without documented NMOU.

Results: Charts of 46 patients were reviewed. Although NMOU contributed to opioid-related healthcare encounters, their onset was often related to poorly controlled pain, declining functional status, and disease progression. NMOU behaviours were documented for 16 (35%)

patients. The most common NMOU behaviour was overuse of prescribed medications, which was documented for 12 patients. For 7 patients, there were indications of use of opioids for psychological coping, including 3 encounters caused by intentional overdoses with suicidal intent. Patients with NMOU were significantly more likely to have a history of substance use, mental illness, and limited social support.

Conclusion: Approximately 1-in-3 patients experiencing opioid-related encounters had indications of NMOU. Further psychosocial care and interdisciplinary pain management are warranted to improve safe opioid prescribing for these patients.

4.2 Introduction

Opioids are commonly used for the management of moderate to severe cancer-related pain,[1] which affects more than a third of patients diagnosed with cancer.[2] As a result, patients with cancer have been found to receive prescription opioids at a rate nearly two times greater than noncancer patients.[3] Beyond the cancer population, prescribing of opioids has been under increasing scrutiny due to harms related to misuse, addiction, and overdose deaths, which have resulted in a public health epidemic across Canada and the United States.[4] However, patients with cancer are thought to be minimally affected by this epidemic, with opioid-related deaths occurring at a rate more than 10 times lower compared to the general population.[5] Furthermore, issues of pain under-treatment and opioid access continue to be concerns for patients with cancer.[6] Despite concerns related to under-utilization of opioid drugs for cancer pain, increasing evidence has been presented that opioid-related harms are of relevance for patients with cancer. Patients with cancer have been found to be at high risk of long-term opioid use which may lead to opioid dependence, tolerance, and increased healthcare utilization.[7–9] Additionally, problems related to nonmedical opioid use (NMOU) are more common than initially reported, with a recent meta-analysis finding a prevalence of 8% among patients with cancer-related pain.[10] NMOU is a term used to describe a variety of opioid misuse behaviours including, opioid use disorders (OUDs), use of prescribed opioids in ways that contravene prescription instructions, or use of opioids based on the feeling or experience they provide beyond analgesia.[11,12]

Although there is increasing recognition of the impact of NMOU and associated adverse outcomes on patients with cancer, few studies have investigated these behaviours among patients with metastatic disease. Assessing the risks of long-term opioid use is particularly complex within this population, as opioid-related harms may be considered as less important when providing pain and symptom management for patients who have limited prognosis and severe pain.[13] However, in a study of patients with advanced cancer, 18% were diagnosed with NMOU in the form of chemical coping,[14] indicating that it is a prevalent issue among patients with metastatic disease. Although patients with cancer may experience NMOU behaviours, the contribution of these behaviours to the incidence of serious opioid-induced adverse effects has not been investigated in this population. Therefore, we aimed to determine whether NMOU was identified as contributing to opioid-related healthcare encounters and investigate the

characteristics associated with NMOU behaviours among patients with metastatic cancer receiving long-term opioid prescribing.

4.3 Methods

4.3.1 Inclusion Criteria

A retrospective longitudinal study design was used to follow patients from the initiation of long-term opioid prescribing until death or the date of data pull (July 2019) for the occurrence of opioid-related encounters. Opioid-related encounters were defined as hospitalizations or emergency department visits with an International Classification of Diseases, 10th edition, (ICD-10) code relating to opioid poisoning/overdose (T40.1-4, T40.6, or X42)[8] or OUD (F11.x).[16] These encounters were identified from the Discharge Abstract Database (DAD) and National Ambulatory Care Reporting System (NACRS) for hospitalizations and emergency department visits, respectively. Patients were identified from the Alberta Cancer Registry (ACR) and were selected for chart review if they 1) were diagnosed with a stage IV solid cancer from 2004-2017 in Calgary or Edmonton, Alberta, Canada and had survival time ≥ 1 year; 2) were opioid naïve at diagnosis; 3) received long-term opioid prescribing (≥90 days of opioid supplied in a 180-day period with a <30 day gap in supply)[15] after diagnosis; and 3) experienced an emergency department visit or hospitalization coded in administrative data as relating to opioid poisoning or OUD following the initiation of long-term opioid prescribing *(Figure 1)*. Patients were defined as opioid naïve if they had not filled any prescriptions for opioids in the 12 months to 31 days preceding diagnosis[9] and did not have any prior diagnoses related to OUD documented in administrative heath data. The study population was limited to patients with chronic metastatic disease by exclusion of patients with less than 12 months of follow-up after diagnosis. Opioid prescriptions from outpatient pharmacies throughout the province were identified from Pharmaceutical Information Network (PIN) data and were considered active for the number of days prescribed following dispensing to the patient.

4.3.2 Chart Review and Data Extraction

Oncology records from two urban cancer centres were accessed through electronic medical records (EMRs). Patient oncology records were reviewed from the time of opioid initiation until the opioid-related encounter. Information was collected from patient charts regarding pain etiology (cancer-related or non-cancer pain, neuropathic component (yes/no), and

location), discussions regarding opioid counselling, and any documentation of patient- or physician-reported NMOU behaviours. Available information on patients' birth country, marital status, social support, mental health, and reported substance use (smoking, alcohol, and recreational drug use) were also captured from oncology records. Hospital records from the opioid-related encounter were reviewed to extract information on symptoms experienced upon admission, factors identified as contributing to the opioid-induced adverse event, treatments received, discharge disposition, documented goals of care, and modifications made to prescription medications. Data extraction was conducted using a standardized form in Microsoft Excel version 2404.

History of mental illness was considered present for patients' whose documented medical history included mention of prior anxiety, depression, other mood disorders, personality disorders, or psychoses.[17] Smoking status was categorized as current smoker, former smoker, or lifetime nonsmoker at the time of the opioid-related encounter and cumulative smoking exposure was quantified in pack-years.[18] History of alcohol misuse was categorized as present for patients with a self-reported history of misuse or heavy drinking recorded in their chart. Social support was categorized as limited if patients self-identified as having an inadequate support system, reported living alone or having unstable living arrangements, or reported significant relational issues with their primary caregiver/spouse.

NMOU behaviours were recorded as being documented in patient charts 1) if patients admitted to misuse or overuse of their opioid medications, 2) if patient caregivers reported opioid misuse or overuse by the patient, 3) if the encounter was a result of an intentional overdose or the patient was found with clear evidence of overuse (e.g., many fentanyl patches on, multiple empty pill bottles, etc.), or 4) if healthcare providers documented multiple instances of drug-seeking behaviours or suspected malingering, including reports of missing or stolen opioid prescriptions, unsanctioned dose increases, early requests for narcotic refills, and/or breaches in signed opioid agreements.[11] Cases wherein it was thought that patient issues understanding prescription instructions or cognitive concerns led to difficulties with prescription self-management and resulted in accidental overuse were not classified as NMOU behaviors despite deviation from prescription instructions.

4.3.3 Data Analysis

Patient characteristics were presented using mean and standard deviation for continuous variables and proportions (%) for categorical variables. Patient characteristics were compared between those with and without indications of NMOU using t-tests for continuous variables and Fisher's exact tests for categorical variables. Inclusion of patients thought to have engaged in accidental overuse in the NMOU group was tested in a sensitivity analysis. All analyses were conducted in StataSE 18.0 using an alpha level of 0.05.

A narrative synthesis was used to describe the symptomatology of and identified contributing factors to opioid-related encounters based on clinician reporting. Indications of NMOU were categorized using a thematic analysis of extracted notes on opioid use behaviours. The resultant non-exclusive categories of NMOU behaviours were 1) use of prescription opioids exceeding the prescribed amount; 2) use of prescription opioids for psychological coping; 3) concerns regarding diversion of prescription opioids; and/or 4) use of illegal, non-prescription opioids.

4.4 Results

There were 46 patients who experienced ≥1 opioid-related encounter following the initiation of long-term opioid prescribing and were eligible for chart review *(Figure 4.1)*.

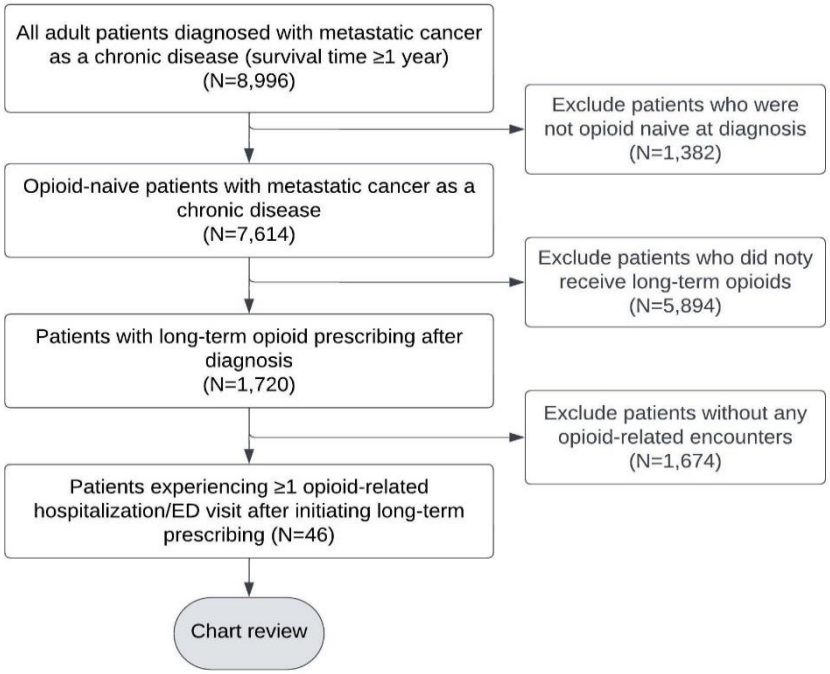

Figure 4.1: Flow Diagram of Patient Eligibility for Chart Review

Demographic and clinical characteristics of included patients are outlined in *Table 4.1*. A majority of patients were male (70%), and the most common primary cancer types were head & neck (28%) or lung (24%). Nearly half of these patients (48%) had a history of mental illness documented in their chart. Issues related to substance use were commonly reported, with 83% being former or current smokers, 41% reporting a history of alcohol misuse, and 17% reporting a history of recreational drug use. Although all patients had a diagnosis of metastatic disease, only 59% of patients had pain which was found to be primarily attributable to malignant causes (i.e., cancer-related). For 24% of patients, their pain was attributed to both malignant and non-malignant causes (i.e., mixed), and for 11% of patients their pain was determined to be non-cancer-related, for example attributable to degenerative changes or traumatic injury. Nearly half of patients (43%) were identified as experiencing neuropathic pain.

Most patients (89%) experienced only a single opioid-related encounter, while three patients experienced two encounters, and two patients experienced three encounters. Therefore, records from 53 opioid-related encounters were reviewed. Of these encounters, 42 (79%) were caused by opioid toxicity. Opioid toxicity leading to delirium or confusion was the most common opioid-induced adverse effect at presentation to the hospital, occurring for 52% of toxicity-

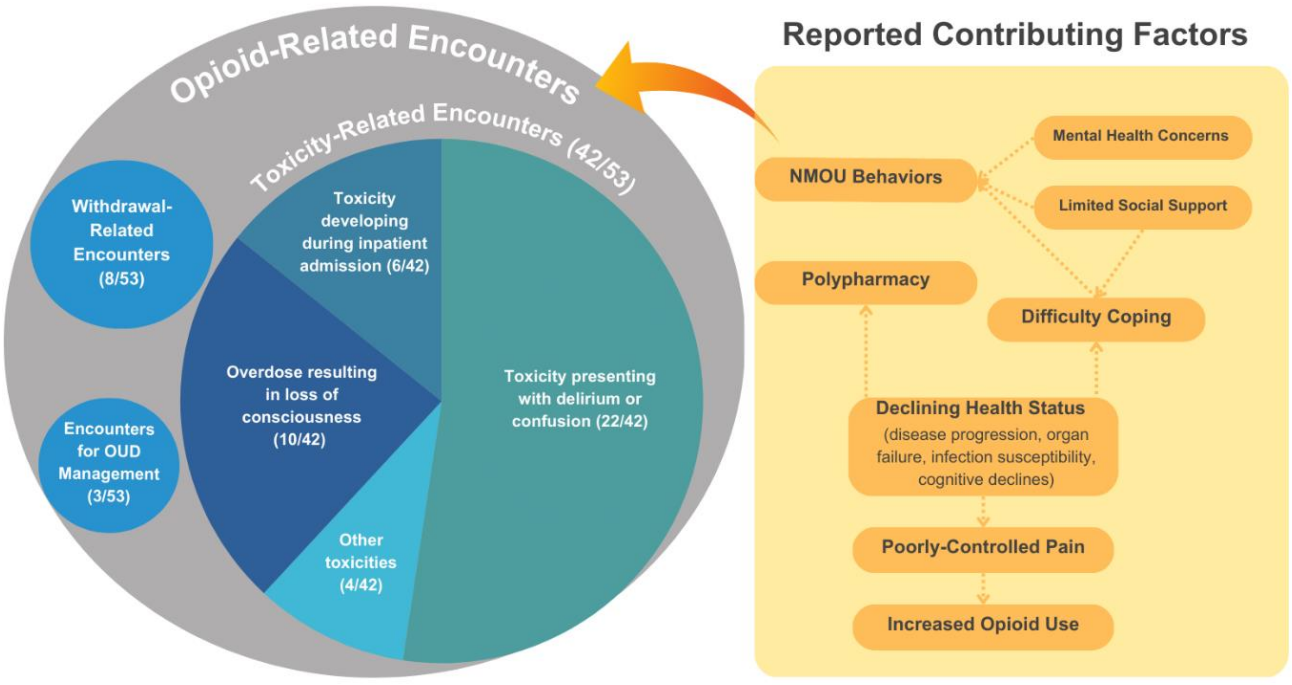

Figure 4.2: Types of Opioid-Related Encounters and Factors Contributing to Their Onset

related encounters. For 10 encounters, opioid overdose occurred in which the patient was found unconscious or unresponsive; all of these encounters required emergency administration of naloxone. In 3 of these encounters, opioid overdose was identified as intentional, and the remaining 7 encounters were thought to be accidental. Although there were 8 encounters in which patients died during their hospital admission, opioid overdose was not recorded as a cause of death for any cases, as patients succumbed to their cancer or other comorbidities. An additional 6 encounters were related to toxicities which developed during inpatient admission but were not noted at presentation to the hospital. Encounters which were not caused by opioid toxicity were encounters related to opioid withdrawal (15%) or encounters for OUD management (6%) (*Figure 4.2)*.

There were 16 patients (35%) found to have documented concerns regarding NMOU. For 15 patients, NMOU concerns related to use of prescription opioids (*Figure 4.3)*; in one case, a patient encounter was caused by non-prescription opioids, wherein the use of illegal street opioids led to overdose. For 14 patients, there was documentation of patients using their prescription medications in amounts greater than prescribed, leading to overuse. Patient reporting

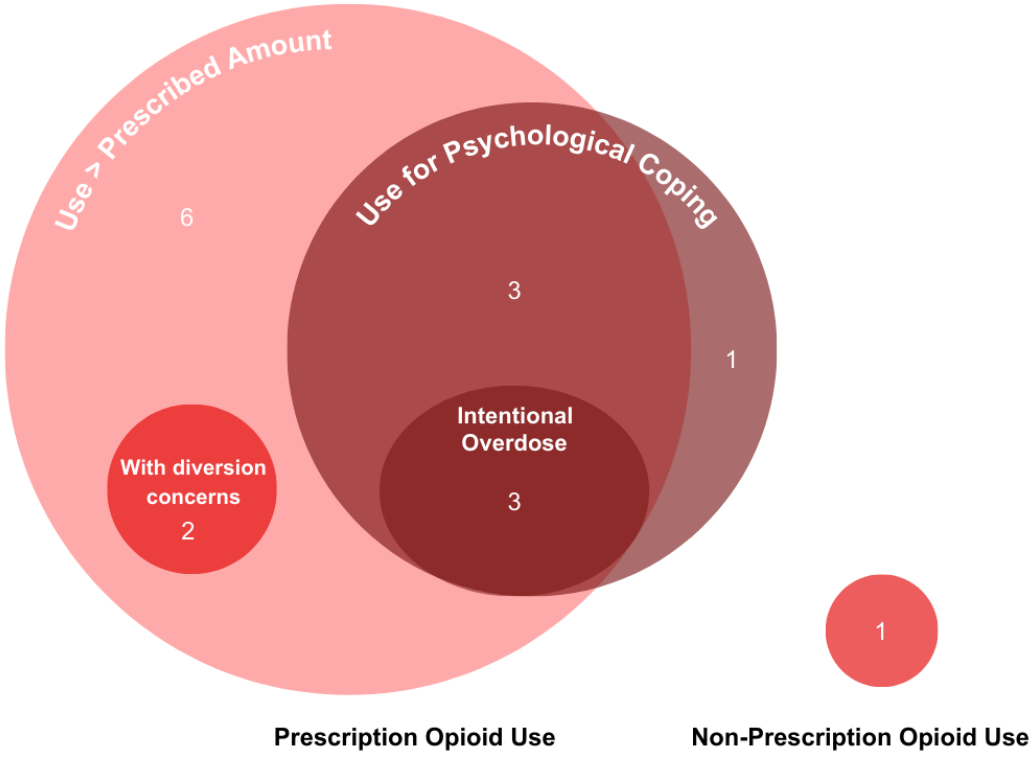

Figure 4.3: Types of NMOU Behaviours Reported Among Patients Experiencing Opioid-Related Encounters while Receiving Long-Term Opioid Prescribing (n=16)

of using prescription opioids for psychological coping was documented in 7 patient charts. In three cases patients had encounters caused by intentional overdose with suicidal intent; other reasons cited for misusing opioids were for managing anxiety, desire to feel sedated, or difficulties coping with their prognosis. Two patients had documented concerns related to opioid diversion, where it was thought that their opioid medications were being used by other individuals. In one case diversion was patient reported, wherein a family member had been appropriating the patient's medication. In the other case, high diversion risk was identified by the healthcare provider based on suspicions that the patient was giving away their prescription medications.

Younger age, having limited social support, being unmarried, being a current smoker, or having a history of recreational drug use were all significantly associated with documented NMOU behaviours (*Table 4.2)*. Although not statistically significant, patients with NMOU were more likely to have a history of mental illness or alcohol misuse. Among patients with NMOU concerns, 69% had a history of mental illness, compared to 37% among patients without documented NMOU concerns (p=0.06). In 4 cases, it was thought that patients engaged in accidental overuse due to cognitive concerns or difficulties with medication management; inclusion of these patients in the NMOU group did not impact observed associations with patient characteristics, with the exception of alcohol misuse (p=0.04), mental illness (p=0.02), and neuropathic pain (p=0.04) being significant, and smoking status being insignificant (p=0.09) (*Table A2.1*).

In contrast to patients thought to be engaging in NMOU behaviours, most patients (65%) were thought to be using opioids in line with medical advice. Among encounters caused by opioid toxicity, 12 (29%) patients had reported pain crises which led to increased use of breakthrough medications or recent dose escalations. In a majority of cases, opioid-related encounters led to palliative care access, with 11 encounters where patients were treated in a palliative care unit, 23 encounters with ≥1 palliative care consult, and 7 encounters resulting in patient transfer to hospice care. Additionally, for 25% of all encounters, patients had documented goals of care focused on comfort and maximal symptom control. Among encounters where patients presented with delirium or confusion, this adverse effect was commonly thought to be multifactorial, noted as relating to dehydration, infection, disease progression, and/or

polypharmacy in 36%, 23%, 18%, and 14% of these encounters, respectively. In 3 encounters, patients entered a withdrawal state after discontinuing opioids due to adverse effects related to their use. In 3 other withdrawal-related encounters, patients expressed that they had reduced their dose due to a personal desire for taking fewer opioids. There were 2 opioid-related encounters thought to be caused by prescriber errors: incorrect conversion when switching opioids in 1 case, and incorrect dispensing of opioid medications in the other.

4.5 Discussion

This retrospective study of patient charts found that approximately 1-in-3 patients with metastatic disease who experienced opioid-related healthcare encounters after receiving long-term opioid prescribing had documented indications of NMOU. These findings reinforce previous literature suggesting that NMOU is a relevant issue for patients with metastatic disease,[14] despite their high symptom burden and need for pain relief.

A number of tools have been created which have been used for assessing the risk of NMOU in patients with cancer.[19] Our findings support the possible utility of these tools for patients with metastatic disease, as established risk factors for NMOU, including history of substance use or mental health concerns, were consistent with those found in our study.[20,21] Furthermore, our findings show that NMOU behaviours can result in the development of adverse effects that lead to healthcare utilization. Standardized risk assessment for NMOU may be useful to identify patients who are at greater risk of opioid-related harms and thereby require more monitoring during long-term opioid prescribing.[12] However, commonly used tools, such as the Opioid Risk Tool (ORT) and Screener and Opioid Assessment for Patients with Pain (SOAPP), require validation for patients with metastatic cancer and the development of tools specific for palliative care patients may be beneficial.[22]

Additionally, safe opioid prescribing may be improved by increased education on opioid safety and co-prescribing of naloxone, which may reduce the burden of opioid overdose among these patients. Our study found that nearly 20% of opioid-related healthcare encounters in this setting were caused by severe overdose requiring emergency administration of naloxone by healthcare teams. Standard co-prescribing of naloxone for palliative care patients with cancer receiving opioids has been shown to be feasible and well-received by both providers and patients.[23] Furthermore, a number of studies have demonstrated that co-prescription of naloxone

to patients being treated with opioids may reduce opioid-related healthcare encounters,[24–26] however, the effectiveness of these harm-reduction strategies need to be investigated among patients with cancer, particularly in palliative care settings.

Additional considerations for harm-reduction in this population include targeting the psychosocial determinants of NMOU. Patients with identified NMOU behaviors may benefit from increased psychosocial care, as their use of opioids was documented as being motivated by psychosocial concerns and/or non-physical pain & suffering among 15% of patients in our study. Previous research has described a potential bi-directional and reinforcing relationship between mental health concerns and opioid use,[27–29] as studies have found that increased psychological distress can worsen pain experience or lead to chemical coping,[30,31] and opioid use can itself increase the risk of developing or worsening mental health disorders.[32–34] Furthermore, our study found that limited social support was associated with NMOU behaviours and was an identified contributing factor to the incidence of opioid-related healthcare encounters. Previous literature in non-cancer populations has demonstrated that social support interventions can improve outcomes for patients being treated for OUD.[35] These findings emphasize the importance of interdisciplinary team involvement for patients receiving opioids for pain management [12], which may help to address mental health and social concerns that are associated with NMOU behaviours and have been found to lead to increased risk of overdose.[36]

Notably, our study found that 6% of opioid-related healthcare encounters were caused by intentional overdose with suicidal intent. Interestingly, all intentional overdose events within our study occurred prior to the introduction of medical assistance in dying (MAiD), which was legalized across Canada in June 2016.[37] The impact of providing MAiD as an option for patients facing terminal diagnoses on opioid-related healthcare encounters within this population was not assessed in our study and requires further investigation. As the period of study primarily occurs in a period where MAiD was not available, this may partially limit the generalizability of our findings to contemporary patients in Canada but may have relevance to regions where MAiD is not available. In spite of this limitation, our findings demonstrate that patients in this population are facing difficulties with suffering and total pain that should be addressed by not only the management of physical symptoms, but also psychological, social, and spiritual concerns.[38] Patients experiencing suicidal ideation should be closely monitored when self-managing opioid

medications and be provided increased psychosocial care targeting suicidal ideation. More research is needed to understand effective interventions for prevention of suicidal behaviours.[39]

Although our study focused on identifying patients with NMOU behaviours, most patients experienced opioid-related encounters despite apparently using opioids in line with medical instruction. These patients were generally facing rapidly declining health status as they approached end-of-life and may benefit from adjustment of prescribing practices and increased counselling on how opioid metabolism may be affected by co-prescribed medications, infection, and organ impairment/failure.[40] Furthermore, opioid toxicity co-occurring with a decline in physical function may serve as an indicator of patients requiring increased involvement from palliative care teams.[41]

Additionally, these events are often related to poorly controlled pain and efforts should be made to help patients engage in effective pain self-management. Many patients had goals of care which prioritized pain control and comfort care, making opioids an essential medicine in a treating clinician's toolkit.[42] In this setting, effective pain management can be negatively impacted by opioid stigma,[43] which was evident among patients in this study. For example, patients commonly expressed elevated concerns regarding the use of opioids, family members commonly identified patients who were reluctant in their use of opioids, and in some instances healthcare providers counselled patients to be more liberal in their use of opioids to adequately manage their pain. Additionally, a number of reviewed encounters were potentially causally related to opioid stigma, as patients self-initiated dose reductions leading to withdrawal, or demonstrated hesitancy in opioid usage which may have led to poor pain control and acute high dose use during pain crises, ultimately resulting in toxicity. As such, it is important that clinicians recognize that while NMOU behaviours are relevant and should be assessed in this population, opioid counselling should be provided in a non-stigmatizing manner which recognizes patients' right to pain relief and encourages effective self management which does not exclude the use of opioids.[6,43]

Limitations:

This study has a relatively small sample size and may not be adequately powered to detect significant differences between subgroups. Furthermore, the sample is limited to patients experiencing serious opioid-induced adverse effects during long-term opioid prescribing;

therefore, our study may identify a higher prevalence of NMOU compared to the wider population of patients with metastatic cancer. Additionally, NMOU was identified based on clinician documentation in medical records and we were unable to obtain data from patients' primary care encounters. As such, there was a variable and limited amount of information on patients' opioid use behaviours, potentially leading to an underestimation of the number of patients who were engaging in NMOU behaviours. Furthermore, the identification of NMOU behaviours may be influenced by clinician bias, as providers may have increased vigilance and suspicion of NMOU among patients with differing socioeconomic status or racial identity.[44,45] Studies with standardized follow-up and assessment for NMOU may provide a more accurate estimate of the prevalence of NMOU in this setting.

Conclusions:

NMOU behaviours can contribute to healthcare utilization among patients with metastatic cancer being prescribed long-term opioids through opioid-related harms such as toxicity, overdose, and OUDs. However, a majority of opioid-related encounters are not primarily attributable to NMOU in this setting. While risk assessment for NMOU is important, it should be conducted in a non-stigmatizing manner which encourages patients to prioritize effective management of their pain. For patients thought to be engaging in NMOU behaviours, increased psychosocial support and mental health monitoring should be offered to address the causes leading to opioid misuse.

Data Availability:

All data used for the analyses in this paper were abstracted from provincial administrative data sources in Alberta, Canada.

Tables

Table 4.1: Demographic and Clinical Characteristics of Patients

Demographic or Clinical Variable	Mean (SD) or Number of Patients (%)
Age at Diagnosis (years)	59.7 ± 12.8 (range: 25, 84)
Sex	
Male	32 (70%)
Female	14 (30%)
Primary Cancer Type	
Head & Neck	13 (28%)
Lung	11 (24%)
Prostate	8 (17%)
Colorectal	6 (13%)
Breast	3 (7%)
Gastroesophageal	3 (7%)
Bladder	1 (2%)
Kidney	1 (2%)
Birth Country	
Canada	30 (65%)
Other	7 (15%)
Not specified	9 (20%)
Marital Status	
Married/Common-Law	25 (54%)
Divorced	8 (17%)
Widowed	8 (17%)
Single	5 (11%)
Limited Social Support	20 (43%)
Smoking Status	
Nonsmoker	8 (17%)
Former smoker	23 (50%)
Current smoker	15 (33%)
Smoking Exposure	
Never Smokers (0 pack-years)	8 (17%)
Light Smokers (1-20 pack-years)	16 (35%)
Moderate Smokers (20-40 pack-years)	8 (17%)
Heavy Smokers (>40 pack-years)	11 (24%)
Not Specified	3 (7%)
History of Alcohol Abuse	19 (41%)
History of Recreational Drug Use	8 (17%)
History of Mental Illness	22 (48%)
Pain Etiology	
Cancer-related pain	27 (59%)
Non-cancer pain	5 (11%)
Mixed	11 (24%)
Unclear	3 (7%)
Identified Neuropathic Pain Component	20 (43%)

Table 4.2: Univariate Analysis of Association between NMOU Behaviours and Patient Characteristics [a]

	Patients with documented NMOU	Patients without documented NMOU	p-value
N	16	30	
Age at Diagnosis	52.3 ± 9.1	63.7 ± 12.7	0.003*
Sex			0.739
Male	12 (75%)	20 (67%)	
Female	4 (25%)	10 (33%)	
Primary Cancer Type			0.092
Head & Neck	7 (44%)	6 (20%)	
Lung	3 (19%)	8 (27%)	
Prostate	0 (0%)	8 (27%)	
Colorectal	4 (25%)	2 (7%)	
Breast	1 (6%)	2 (7%)	
Gastroesophageal	1 (6%)	2 (7%)	
Bladder	0 (0%)	1 (3%)	
Kidney	0 (0%)	1 (3%)	
Birth Country			0.383
Canada	12 (75%)	18 (60%)	
Other	1 (6%)	6 (20%)	
Marital Status			0.005*
Married/Common-Law	4 (25%)	21 (70%)	
Divorced, Widowed or Single	12 (75%)	9 (30%)	
Smoking Status			
Lifetime Nonsmoker	2 (13%)	6 (20%)	0.007*
Former Smoker	4 (25%)	19 (63%)	
Current Smoker	10 (63%)	5 (17%)	
Smoking Exposure Level			
Never Smokers (0 pack-years)	2 (13%)	6 (20%)	0.123
Light Smokers (1-20 pack-years)	5 (31%)	11 (37%)	
Moderate Smokers (20-40 pack-years)	6 (38%)	2 (7%)	
Heavy Smokers (>40 pack-years)	3 (19%)	8 (27%)	
History of Alcohol Abuse			0.058
Reported	10 (63%)	9 (30%)	
Not reported	6 (38%)	21 (70%)	
History of Recreational Drug Use			0.001*
Reported	7 (44%)	1 (3%)	
Not reported	9 (56%)	29 (97%)	
Limited Social Support			<0.001*
Reported	13 (81%)	7 (23%)	
Not reported	3 (19%)	23 (77%)	
History of Mental Illness			0.063
Reported	11 (69%)	11 (37%)	
Not reported	5 (31%)	19 (63%)	
Pain Etiology			0.190
Cancer-related pain	7 (44%)	20 (67%)	
Non-cancer pain	1 (6%)	4 (13%)	
Mixed	6 (38%)	5 (17%)	

Neuropathic Component			0.117
Reported	4 (25%)	16 (53%)	
Not reported	12 (75%)	14 (47%)	

[a] Not specified or unclear treated as missing data for comparing patient characteristics

4.6 References

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CHAPTER 5: CONCLUSIONS AND FUTURE DIRECTIONS:

5.1 Summary of Key Findings

This thesis presents three studies focusing on opioid prescribing for patients who are living with chronic metastatic cancer. Patients living with chronic metastatic disease face distinct challenges related to having terminal, incurable diagnoses while existing in a state of limbo where they may have to live with cancer and its effects for years.[16] Metastatic disease often results in severe pain which can negatively impact QoL, and which should be managed and treated accordingly.[32] The goal of pain management in this setting centers on giving patients the opportunity to continue living their lives *with* cancer, rather than having cancer become their life.

The first study used a narrative review of existing literature to contextualize and characterize how perceptions of opioid use may act as a barrier to optimal pain management for patients with metastatic disease. The review demonstrated that the stigmatization of opioid use leads to unnecessary opioid-restricting behaviours and in turn causes less successful pain self-management and impairs patients' ability to live well. The review further highlighted knowledge gaps in existing literature relating to the risks of opioid prescribing for these patients. Most notably, the literature does not contain any population-based estimates of long-term opioid use in patients with metastatic cancer. Furthermore, risks commonly associated with long-term opioid use are poorly characterized in this population, with no studies available on opioid-related hospitalizations, and limited studies on NMOU. Inability to provide patients with this information may lead to exaggerated fears regarding opioid use and may contribute to increased uncertainty and anxiety, rather than facilitating informed decision-making by patients regarding their opioid use.

Related to identified knowledge gaps, the second study used retrospective data to report a population-based estimate of long-term opioid prescribing. This study found that patients living with chronic metastatic cancer were commonly recipients of long-term opioid prescribing, with 23% of included patients being affected. Although long-term prescribing was found to occur at a higher rate than that reported in other cancer populations,[97,99,106] our findings indicate that in most cases it was employed during the EoL phase of disease. These findings agree with previous research which reports increases in opioid prescribing near the EoL. Within this phase, patients often face deteriorating health status and increasingly burdensome symptoms.[129,130] As such,

opioid prescribing may be appropriately initiated by clinicians who recognize patients with an increased need for pain and symptom management. This may additionally help explain the observed increase in opioid dosage over the course of long-term prescribing, which may be caused by difficult-to-treat and progressively worsening pain associated with disease progression;[87] these factors should be considered as potential contributors to dose escalation in addition to cases of opioid tolerance or OIH which may be related to long-term prescribing.[86]

This study further found that recipients of long-term opioid prescribing were at risk of experiencing healthcare encounters related to opioid overdose or OUD, with 3.4% of long-term opioid prescribing recipients experiencing hospitalizations or emergency department visits of this type. While this was the first study specifically reporting encounters among patients with metastatic cancer, the rate of opioid overdose events was higher than that reported in previous literature among patients with cancer.[105] The incidence of opioid-related encounters was found to increase with higher opioid dosage, as well as with concurrent prescribing of benzodiazepines, anxiolytics, antidepressants, and neuroleptics. As such, the high rate of opioid-related encounters may be related to increased pain, health deterioration, and higher rates of psychoactive drug use or polypharmacy which are pertinent concerns for patients with metastatic disease, especially as they near EoL.

The third and final study described a subset of the opioid-related healthcare encounters identified from the population-based study. For nearly half of reviewed encounters, the adverse effect leading to opioid-related hospitalization or emergency department visit was confusion or delirium thought to be related to opioid toxicity. However, this type of event was commonly identified as being multifactorial, related to polypharmacy, preexisting cognitive concerns, disease progression, and/or dehydration in many cases. The remaining opioid-related encounters were caused by overdose resulting in loss of consciousness (20%), withdrawal-related encounters (16%), toxicities developing over the course of an inpatient admission (12%), encounters for the management of OUD (6%), and other toxicities at presentation to the hospital (4%).

Based on reporting from oncology and hospitalization or emergency department records, 35% of patients who experienced an opioid-related encounter had documentation of NMOU behaviours in their charts. Patients with identified NMOU behaviours were more likely to have limited social support, to have a history of substance dependence, or other mental health

concerns. This study agrees with published literature as it verifies the idea that NMOU is an applicable issue for patients with metastatic cancer[112] and risk factors are consistent with those used in tools for identifying patients at risk of NMOU.[131] In addition to NMOU behaviours, declining health status, polypharmacy, and poorly controlled pain were identified as significant contributing factors to the occurrence of opioid-related encounters. In contrast to patients displaying NMOU behaviours, many patient records included notes which suggested experiences related to opioid stigma. In line with findings of the initial narrative review, patients were often hesitant in their use of opioids, expressing that they often restricted their use until their pain became unbearable. These manifestations of opioid stigma were additional contributors to the occurrence of opioid-related healthcare encounters, as they contributed to both unsanctioned dose reductions which resulted in withdrawal, or pain which was poorly controlled due to opioid-restricting behaviours, eventually resulting in severe pain and acute use of high dose opioids, which led to toxicity.

5.2 Challenges in Examining Opioid Use for Patients with Metastatic Cancer

It is well recognized that patients with metastatic cancer are in need of palliative care and have a right to pain relief.[19] Patients living with chronic metastatic cancer exist in a unique space which bridges divides between treatment paradigms for chronic pain, cancer pain, and EoL care. Previously identified differences when comparing the treatment of chronic pain to pain at the EoL include reduced concerns about tolerance and dependence, increased medical supervision, and a balance of harm-to-benefit that is more tolerant of potential harms.[132] Where patients living with chronic metastatic cancer fall on this spectrum is unclear. These patients face terminal but often uncertain prognosis times and have pain which may last for years but will ultimately transition from the context of 'pain during living' to the context of 'pain during dying.'[132] The timing of this transition is not easy to identify, particularly when using retrospective data which has limited granularity. While definitions of EoL care have been set at 1-year before death in our study of long-term opioid prescribing, the process of dying and receiving EoL care for some patients may occur within months, weeks, days, or even hours before death. On the flipside, clinical guidelines recommend early access to palliative care for all patients with advanced stage disease,[19] such that patients with chronic metastatic cancer may receive palliative care for years before death. As such, the transition of patient goals of care to reflect palliative-intent, rather than

proximity to EoL, may be a more accurate indicator of the timing in which opioids may be considered as an essential medicine and concerns regarding the appropriateness of prescribing practices are less pertinent. While these changes in goals of care were not captured in administrative data sources, we were able to consider these factors when reviewing patient medical records of opioid-related encounters in the subsequent study.

Furthermore, there remain uncertainties surrounding what constitutes optimal opioid prescribing practices for patients with chronic metastatic disease. While there are a number of patients who certainly benefit from long-term opioid prescribing and the proportion of patients requiring opioids increases near EoL, the proportion of patients who should receive opioids, particularly over an extended timeframe, is not clear.[6] As a result, it is difficult to assess the appropriateness of opioid prescribing practices in this setting. While this research demonstrated some indicators of clinically warranted opioid prescribing, including increased prevalence nearing EoL and among patients with bone metastases, we were unable to assess whether these prescribing practices were reflective of over-prescribing, under-prescribing, or safe and effective management of cancer pain in this setting.

Additionally, our findings are limited in that they rely on practitioner reporting and documentation. In the second paper, which made use of administrative health databases, opioid-related healthcare encounters were identified using ICD-10 classification codes which identify diagnoses, conditions, problems or circumstances of the patient during their hospital stay or emergency department visit. This method is likely to underestimate the incidence of opioid-related encounters due to use of non-specific classifications or use of a single code to account for polysubstance overdose.[133] In our subsequent review of patient charts, it was additionally revealed that opioid-related encounters were inconsistently coded using different ICD-10 codes for similar events (e.g., toxicity leading to confusion was variously coded as acute intoxication, other mental or behavioural disorders, and opioid poisoning). Due to the use of retrospective administrative health data, we were unable to provide a description of the type of opioid-induced adverse effects experienced by patients, as well as their severity. While this limitation was addressed in part within the third study, which used chart review methods to extract more detail on the opioid-related encounters, only a subgroup of the overall population was selected for chart

review, and these findings may have limited applicability to patients receiving care in rural settings.

Reporting bias was also present in our chart review study, as risk assessment for NMOU was not routinely implemented and identification of NMOU behaviours relied on subjective and inconsistent reporting by healthcare providers. Within our study, some patients had regular and repeated follow-up with oncologists and cancer pain management teams leading to significant documentation of opioid counselling and adherence with prescription instructions. However, there were a number of patients in our study who had pain management plans led by primary care or non-oncology physicians who's notes and records were not available for review in our study. This was particularly pronounced among patients who had pain which was not attributable to cancer-related causes, as these patients were not eligible to receive care from cancer pain management clinics and were commonly referred to their family doctor for pain management. This likely lead to underestimation of the prevalence of NMOU behaviours which may have gone undetected for patients who had reduced involvement from oncology providers.

Additionally, there is the possibility that some patients were misidentified by providers as engaging in NMOU behaviours. The identification of NMOU by practitioners may be influenced by bias, particularly for patients with co-existing social or financial concerns. The literature review included in this thesis revealed that opioid stigma commonly follows social structures such as race and socioeconomic status, and patients who fall into these groups may be more likely to be identified as engaging in NMOU behaviours. Behaviours associated with 'drug-seeking,' such as early refill requests, may be associated with poorly controlled pain which may require increased opioid dosage, rather than indicating prescription overuse. While this potential misclassification may have an impact on our findings, the magnitude of the impact is likely very small, as in a majority of cases NMOU behaviours were admitted by patients or were corroborated by caregivers/family members who expressed concerns about opioid misuse.

While the population-based estimate of long-term prescribing practices should have relatively strong generalizability to patients in Alberta, its main limitation relates to timeliness, as patient data was only collected up until July 2019. This is potentially of relevance as previous studies have indicated longitudinal changes in opioid prescribing among patients with metastatic cancer. There have been reported declines in prescribing to patients with metastatic disease,[134–136]

and patients with bone metastasis were reported to receive significantly fewer opioids from 2011 to 2017, in terms of both proportion of patients receiving prescriptions as well as dosage level.[137] Our study did not specifically investigate trends in prescribing over time and there are currently no reports outlining prescribing trends among patients in Alberta during the study period or afterwards. If prescribing practices have declined in Alberta in recent years, our study may overestimate the proportion of patients receiving long-term prescribing in contemporary care settings; this requires further investigation. The reported downward trend in prescribing may be related to stigmatization of opioid use, public health concerns regarding overprescribing in noncancer settings, greater implementation of risk assessment for NMOU, and/or greater reliance on nonpharmacological interventions for pain management. Additionally, the COVID-19 pandemic may have had a significant impact on the provision of pain and symptom management for these patients, and these changes have not been investigated. During the COVID-19 pandemic, opioid-related overdose events and deaths significantly increased;[138] however, whether patients with cancer experienced similar changes is unclear.

5.3 Implications for Clinical Practice

This research supports a growing body of evidence suggesting that long-term opioid prescribing impacts a large proportion of patients with cancer, and these patients are at risk of opioid-related harms including overdose, increased healthcare utilization, and NMOU. Previous literature suggests that about 1-in-5 patients with cancer pain are at risk of NMOU.[91,139] Due to this evidence, recommendations for cancer pain management have increasingly recognized the importance of including standard risk assessment for NMOU as part of a creating a comprehensive plan for cancer pain management.[81,114] Consistently identified risk factors for NMOU include younger age, mental health history, and history of illegal drug use,[140] which were all associated with NMOU behaviours identified in our study. Tools such as the ORT and SOAPP-SF have been created to allow for standardized and rapid assessment of patients' risk of NMOU,[141,142] although they still require validation in palliative care settings.[118] While these tools were initially developed in noncancer populations, their utility in cancer settings has been demonstrated in a number of studies.[115,116,140]

Despite growing recognition of the importance of opioid risk assessment, these tools are poorly adopted in routine clinical care, with current practice largely reliant on subjective and variable assessments by clinicians. In a cross-sectional survey of oncology providers, 17% of physicians reported rarely assessing for patients' current or past OUD history.[143] This may be additionally complicated by situations in which patients receive opioids from non-oncology providers who may vary in their comfortability and training surrounding safe opioid prescribing. Our findings support the increased use of risk assessment tools by clinicians prescribing opioids for patients with cancer pain. Identification of patients at an elevated risk of NMOU may improve safe prescribing practices for this population, for whom pain management needs are often very complex and should be informed by a benefit-to-harm framework.

Following the identification of patients who are at high risk of engaging in NMOU behaviours, strategies can be implemented to mitigate risk and reduce opioid-related harms. Regardless of their risk of developing NMOU, patients have right to pain relief and clinicians should aim to provide supportive care which alleviates patient pain and aims to maintain or improve QoL in the safest way possible. This may be achieved using strategies to increase opioid monitoring, such as weekly or daily dispensing, assigning a sole opioid prescriber through collaboration between oncology, palliative care, and primary care teams, creating opioid agreements/contracts, and/or implementing urine drug screens.[143] Furthermore, our research suggests that patients engaging in NMOU behaviours may benefit from increased psychosocial support, as their opioid use was identified as relating to psychological and social concerns. Therefore, connecting patients with social workers, psychologists, or addiction specialists may help to address the upstream determinants of patients' NMOU behaviours. The development and implementation of interdisciplinary oncology teams to support patients' supportive care needs may help to address the factors contributing to the occurrence of serious opioid-induced adverse effects among patients receiving long-term opioid prescribing.

Additionally, patients receiving long-term opioid prescribing may benefit from increased education on opioid safety and increased implementation of harm-reduction strategies. Among patients with advanced cancer, the provision of educational materials on opioid safety has been shown to improve safe use of opioid medications.[144] In addition to providing education resources, providers may be able to impact overdose risk through prescribing practices which

focus on harm-reduction. The relatively high burden of overdose observed in our study may be addressed in clinical settings by implementing standard co-prescribing of naloxone for patients with cancer receiving high dose opioids, which has been shown to be feasible and well-received by both providers and patients.[145] Additionally, clinicians should attempt to incorporate nonpharmacological interventions into patient pain management plans, and consider dose reductions if patients are able to obtain acceptable pain relief from nonpharmacological treatments.[72,146] Clinicians should consider the incorporation of evidence-based nonpharmacological interventions, such as physiotherapy,[73] mind-body therapies or mindfulness interventions,[75,147] or other integrative interventions,[72,74,148] dependent on patient preferences, functional status, pain characteristics, and cancer type. Furthermore, efforts to discontinue unnecessary medications may be warranted, as our study found an association between prescribing of psychoactive medications and overdose risk. Reported rates of polypharmacy are high and prescribing of low or limited use medications is common among patients with advanced cancer.[149] Identification of inappropriate drug prescriptions can be highly effective for reducing polypharmacy and may be led by oncologists or with increased involvement from palliative care physicians.[150,151] Similarly, de-prescribing of benzodiazepines may help to reduce the risk of opioid overdose and should be considered for patients with metastatic cancer who are receiving opioids.[152,153] Opioid rotation may be beneficial to reduce MEDD or to switch to opioids which are less prone to misuse, such as LA formulations, methadone, or buprenorphine.[119] Although clinicians may be aware of these options, specific tools to identify patients at risk of opioid-related harms and notify clinicians of potential options for harm-reduction or de-prescribing may be useful increase their uptake in routine care.

Opioid-related healthcare encounters were additionally found to be temporally related to EoL, with over a third of encounters occurring in the last 90-days of life. In reviewing patient charts, declining health status as patients approached death was identified as a contributing factor to experiencing an opioid-related healthcare encounter. As such, clinicians should monitor patients for signs of shortened prognosis,[154] and patients identified as being near EoL who are self-managing their opioids may require increased monitoring for signs of toxicity. As advanced cancers progress, patients increasingly experience acute medical issues like delirium, sepsis, and organ dysfunction which may increase their susceptibility to overdose.[155,156] Furthermore, opioids are known to provoke or prolong delirium and hallucinations, with severe, multifactorial

manifestations more common among patients with advanced cancer compared to patients with earlier stage disease.[157] In response to changes which may accompany the EoL phase of disease, prescribing clinicians may consider tailoring opioid prescribing to patients with deteriorating functioning and health; for example making dose adjustments for patients with renal or hepatic impairment and engaging in increased monitoring of patients with dementia or other cognitive concerns.[158] While these risk factors may be well-known by clinicians practicing pain management, particularly in a palliative care setting, our findings demonstrate that patients in outpatient settings may not be identified as experiencing these declines prior to experiencing a serious adverse effect. As such, increased monitoring from clinical teams, perhaps utilizing home care or telehealth resources, should be considered for patients receiving long-term opioid prescribing in this context.

5.4 Future Research Directions

The available literature on opioid prescribing for patients with chronic metastatic cancer remains sparse, with many unexplored topics in areas of metavivorship experiences, benefit-to-harm assessment for patients with uncertain prognosis and terminal diagnosis, and strategies to effectively improve opioid safety for these patients. Firstly, future studies should aim to better understand priorities and decision-making for patients living with metastatic cancer as a chronic disease. These patients do not neatly fit into traditional cancer care narratives which center on 'fighting for a cure,' 'not giving up,' and surviving cancer, as opposed to living *with* cancer. As such, it is important to investigate what factors patients identify as benefiting their QoL in light of ongoing treatment, potential cancer progression, and coping with limited prognosis. These priorities may lead to differential considerations of the risks of opioid use; it has been suggested that chronic risks such as dependence and tolerance have less relevance to patients with metastatic disease, however this has not been sufficiently explored from the perspective of the patient living with chronic incurable cancer. Qualitative investigations and mixed-methods studies may be useful for better understanding the patient perspective of the trade-off between opioid analgesia and potential for adverse outcomes among patients living with chronic metastatic disease.

Additionally, greater research is needed to inform the assessment of appropriate prescribing practices for patients with chronic metastatic cancer. The extent to which long-term opioid prescribing benefits patients in terms of outcomes such as pain reduction, physical function, and QoL are not clear. Based on existing clinical care guidelines and designation of opioids as essential medicines,[46,70] randomized trials to assess opioid efficacy are not justified. However, well designed prospective studies which match patients based on relevant clinical, demographic, and pain-related characteristics, as well as monitor patient-reported outcomes over time, may be useful to understand the long-term efficacy of opioids for the treatment of chronic cancer-related pain. Studies of this type may additionally be beneficial in determining the extent to which dose escalation over the course of long-term prescribing is related to disease progression, opioid tolerance, and OIH.

Although it is increasingly clear that NMOU is a relevant issue for patients with cancer, there is very little evidence on effective strategies for reducing these behaviours among patients with cancer, particularly in the context of patients with severe or chronic cancer pain. Additionally, further research is needed to design and validate risk assessment tools tailored to palliative care populations.[118] Although recommendations for clinical management of NMOU in this setting recommend risk mitigation, harm-reduction, and strategies for addressing the psychosocial determinants of NMOU,[119] there is very limited evidence regarding 1) whether these strategies are routinely implemented in different areas of clinical care and which providers should be responsible for various aspects of NMOU management, 2) how to encourage effective implementation of these strategies within complex care systems, and 3) what specific interventions are effective in reducing NMOU behaviours, as well as resultant adverse outcomes. For example, there is preliminary evidence suggesting that co-prescribing of naloxone may reduce the incidence of opioid-related healthcare encounters,[159,160] however this has not been formally investigated within cancer populations.

Furthermore, it is recognized that NMOU commonly co-occurs with social and psychiatric concerns which may cause or exacerbate these behaviours.[161] Interdisciplinary team involvement and increased access to psychosocial resources have been recommended in these cases,[119] but specific interventions have not been rigorously tested and explored. In noncancer settings, the use of cognitive behavioural therapy has been shown to be effective for the

treatment of substance use disorders,[162] but has not been specifically investigated in cancer settings, let alone specifically for patients with metastatic disease. While some studies have demonstrated feasibility and acceptability of psychosocial interventions for patients with cancer and high NMOU risk,[163] studies describing the effectiveness of these methods for treating NMOU and OUD among patients with cancer are needed.

In addition to NMOU, deteriorating health status and physical functioning near the EoL were identified as contributing factors to experiencing opioid-related healthcare encounters in this setting. While some of these events may be inextricably linked to factors which are difficult to target, such as terminal delirium, it is possible that increased monitoring of patients' concomitant health concerns near EoL, such as renal impairment, infection susceptibility, and cognitive concerns, may allow for greater individualization of opioid counselling. This may be facilitated by the implementation of tools which predict patient prognosis and prompt increased palliative care involvement for patients nearing EoL.[164,165] Whether these strategies have the potential to improve safe opioid prescribing and reduce the incidence of opioid-related encounters near EoL requires investigation.

5.5 Conclusion

The overall purpose of this research was to examine long-term opioid prescribing and risks related to these prescribing practices among patients living with metastatic cancer as a chronic disease. Three interrelated investigations were carried out in relation to this overall purpose. To our knowledge, we provided the first population-based estimate of long-term opioid use among patients living with chronic metastatic cancer. Furthermore, the population-based data suggested that recipients of long-term opioid prescribing were at a relatively high risk of experiencing hospitalizations or emergency department visits related to opioid overdose or OUD. Findings from detailed chart review of these opioid-related encounters revealed that more than a third of patients experiencing encounters related to opioid overdose or OUD had documented NMOU behaviours. Collectively, these findings elaborated on the nuanced and complex balance surrounding opioid prescribing in this setting, where chronic pain intersects with EoL care and opioid stigma needs to be balanced against the need for risk assessment and harm-reduction. The changing landscape of metavivorship, reliance on opioids to manage cancer pain, and growing

evidence that opioid-related harms impact patients with cancer, point to the need for further investigations into what constitutes ideal opioid prescribing and comprehensive pain management for patients with chronic metastatic cancer, particularly those engaging in NMOU behaviours.

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APPENDICES

Appendix 1: Supplementary Tables for Chapter 3

Table A1.1: Included Primary Cancer Types within the Study Population

Tumor Group	Cancer site	Number of Patients
Lung/Bronchus	Lung/Bronchus	2,164 (19.8%)
Colorectal (n=2,195)	Colon	1,351 (12.4%)
	Rectum	600 (5.5%)
	Rectosigmoid Junction	244 (2.2%)
Prostate	Prostate	2007 (18.4%)
Head and Neck (n=1,657)	Tonsil	440 (4.0%)
	Base of Tongue	329 (3.0%)
	Larynx	148 (1.4%)
	Tongue, other and unspecified	111 (1.0%)
	Nasopharynx	101 (0.9%)
	Parotid gland	80 (0.7%)
	Mouth, other and unspecified	79 (0.7%)
	Oropharynx	73 (0.7%)
	Pyriform sinus	53 (0.5%)
	Floor of mouth	48 (0.4%)
	Gum	44 (0.4%)
	Accessory Sinuses	38 (0.3%)
	Hypopharynx	32 (0.3%)
	Nasal Cavity and Middle Ear	31 (0.3%)
	Palate	23 (0.2%)
	Major Salivary Glands, other and unspecified	15 (0.1%)
	Lip	6 (<0.1%)
	Lip, Oral Cavity, and Pharynx, other and unspecified	6 (<0.1%)
Breast	Breast	949 (8.7%)
Gastroesophageal (n=406)	Stomach	249 (2.3%)
	Esophagus	157 (1.4%)
Kidney	Kidney	303 (2.8%)
Bladder	Bladder	236 (2.2%)
Pancreas	Pancreas	226 (2.1%)
Ovary	Ovary	206 (1.9%)
Endometrium	Endometrium	166 (1.5%)
Cervix	Cervix	103 (0.9%)
Hepatic (n=150)	Liver and Intrahepatic Bile Ducts	82 (0.8%)
	Biliary Tract, other & unspecified	39 (0.4%)
	Gallbladder	29 (0.3%)
Melanoma (n=149)	Melanoma of Skin	122 (1.1%)
	Melanoma, other	23 (0.2%)
	Melanoma of Eye	4 (<0.1%)
Central Nervous System (n=10)	Brain	8 (<0.1%)
	Meninges	1 (<0.1%)
	Spinal Cord, Cranial Nerves and other CNS	1 (<0.1%)

Table A1.2: Morphine Equivalent Dose (MED) Conversions for Prescribed Opioids[1]

Opioid	Conversion factor	Route
Buprenorphine (in mcg/hr)	2.2	Transdermal
Codeine	0.15	Oral
Fentanyl (in mcg/hr) (in mcg/ml)	2.4 0.2	Transdermal Parenteral
Hydrocodone	1	Oral
Hydromorphone	4 17.5	Oral Parenteral
Meperidine	0.4	Parenteral
Methadone 1–20 mg/day 21–40 mg/day 41–60 mg/day ≥61–80 mg/day	 4 8 10 12	 Oral
Morphine	1 3	Oral Parenteral
Oxycodone	1.5	Oral
Oxymorphone	3	Oral
Tapentadol	0.4	Oral
Tramadol	0.1	Oral

[1]Conversion to MED was carried out using the R Package OralOpioids[37] for oral preparations and transdermal fentanyl, and using recommended conversion factors from Neilson et al.[38] for parenteral preparations and transdermal buprenorphine

Table A1.3: Classification of Concurrent Medications according to ATC-Code

Medication Classification	ATC Codes
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)	M01A
Anxiolytics	N05B
Benzodiazepines	N05CD, N05CF
Antidepressants	N06A
Selective Serotonin Reuptake Inhibitors (SSRIs)	N06AB
Tricyclic Antidepressants (TCAs)	N06AA
Neuroleptics	N05A
Haloperidol	N05AD01
Quetiapine	N05AH04

Table A1.4: ICD Codes used for Identifying History of Mental Health Diagnoses

Diagnosis	ICD-10 Codes[1]	ICD-9 Codes[2]
Substance Dependence	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1 F11.x-F16.x, F18.x, F19.x, Z71.5. Z72.2	303.0, 303.9, 304.x, 305.x
Anxiety Disorders	F41.0, F41.1, F41.3, F41.8, F41.9	300.0x
Depressive Disorders	F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2	296.2, 296.3, 298.0, 300.4, 311.0

[1] Used for searching encounters in DAD and NACRS databases; [2] Used for searching encounters from physician claims data.

Table A1.5: Comparison of Patients Identified by Different Long-Term Prescribing Definitions

	Long-term recipients identified by primary definition	Long-term recipients only identified by alternate definition	p-value
N	**2,521**	**329**	
Duration of Prescribing (days)	475.42 ± 439.97	250.21 ± 133.74	<0.001*
Mean MEDD	96.51 ± 144.89mg	93.92 ± 235.10mg	0.845
MEDD at Initiation	63.54 ± 111.93mg	79.86 ± 245.32mg	0.234
Age at Diagnosis	61.88 ± 12.02	64.76 ± 12.85	<0.001*
Vital Status			
Alive	430 (17.06%)	44 (13.37%)	0.108
Deceased	2,091 (82.94%)	285 (86.63%)	
***Survival Time** (days)*	*1025.42 ± 729.42*	*913.73 ± 662.12*	*<0.001**
Sex			
Male	1,500 (59.50%)	184 (55.92%)	0.238
Female	1,021 (40.50%)	145 (44.08%)	
Area of Residence[2]			
Urban	1,839 (72.94%)	280 (85.11%)	<0.001*
Rural	681 (27.01%)	49 (14.89%)	
Tumor Group			
Lung	540 (21.42%)	69 (20.97%)	
Colorectal	481 (19.08%)	72 (21.88%)	
Prostate	504 (19.99%)	37 (11.25%)	
Head & Neck	380 (15.07%)	62 (18.84%)	0.001*
Breast	225 (8.93%)	24 (7.29%)	
Other	391 (19.75%)	65 (19.76%)	
Presence of Bone Metastasis	888 (35.22%)	65 (19.76%)	<0.001*
Year of Diagnosis			
2004-2008	695 (27.57%)	79 (24.01%)	
2009-2013	1,066 (42.28%)	126 (38.30%)	0.020
2014-2017	760 (30.15%)	124 (37.69%)	
History of Mental Health Diagnoses			
Substance Dependence	237 (9.40%)	21 (6.38%)	0.091
Anxiety Disorders	248 (9.84%)	31 (9.42%)	0.889
Depressive Disorders	322 (12.77%)	31 (9.42%)	0.100

Table A1.6: Multivariable Logistic Regression of Factors Associated with Long-Term Prescribing

	Odds Ratio (OR)	95% Confidence Interval	p-value
Age at Diagnosis[1]	0.74	0.71, 0.78	<0.001*
Year of Diagnosis[2]	1.03	1.02, 1.04	<0.001*
Vital Status			
Alive	Reference		<0.001*
Deceased	3.22	2.83, 3.67	
Sex			
Male	Reference		0.04*
Female	1.13	1.01, 1.27	
Area of Residence[2]			
Rural	Reference		0.002*
Urban	0.83	0.74, 0.93	
Tumor Group			
Lung	Reference		
Colorectal	1.22	1.03, 1.45	
Prostate	0.89	0.64, 1.21	<0.001*
Head & Neck	1.54	1.27, 1.87	
Breast	0.56	0.42, 0.75	
Other	0.95	0.81, 1.12	
Presence of Bone Metastasis	2.17	1.90, 2.49	<0.001*
Treatment Received			
Chemotherapy	0.91	0.81, 1.02	0.109
Surgery	0.80	0.72, 0.90	<0.001*
Radiation	1.13	0.99, 1.28	0.062
Hormone Therapy	1.28	0.97, 1.71	0.084
Immunotherapy	0.97	0.76, 1.24	0.832
History of Mental Health Diagnoses			
Substance Dependence	1.28	1.01, 1.62	0.044*
Anxiety Disorders	1.12	0.95, 1.32	0.183
Depressive Disorders	1.57	1.34, 1.82	<0.001*
Neighborhood-level Income			
Lowest Quintile	Reference		
2nd Quintile	1.06	0.91, 1.24	0.775
3rd Quintile	0.96	0.82, 1.13	
4th Quintile	1.00	0.84, 1.19	
Highest Quintile	1.00	0.84, 1.20	
Neighbourhood-level Education			
Lowest Quintile	Reference		
2nd Quintile	0.95	0.82, 1.11	0.944
3rd Quintile	0.97	0.82, 1.14	
4th Quintile	1.00	0.84, 1.18	
Highest Quintile	0.96	0.79, 1.15	

[1] Age at diagnosis was considered as a continuous variable and was scaled into years divided by 10.
[2] Year of diagnosis was considered as a continuous variable for number of years after 2000.

Table A1.7: Sensitivity Analysis for Associations with Long-Term Prescribing Using an Alternate Definition including receipt of >10 prescriptions per year

	Total Cohort	Patients with Long-term prescribing[3]	Patients without Long-term prescribing	p-value
N	**10,927**	**2,850 (26.08%)**	**8,077 (73.92%)**	
Age at Diagnosis	64.01 ± 12.70	61.88 ± 12.02	64.76 ± 12.85	<0.001*
Vital Status[1]				<0.001*
Alive	3,314 (30.33%)	474 (16.63%)	2,840 (35.16%)	
Deceased	7,613 (69.67%)	2,376 (83.37%)	5,237 (64.84%)	
***Survival Time** (days) (among decedents)*	*948.59 ± 685.75*	*1025.42 ± 729.42*	*913.73 ± 662.12*	*<0.001**
Sex				0.145
Male	6,582 (60.24%)	1,684 (59.09%)	4,898 (60.64%)	
Female	4,345 (39.76%)	1,166 (40.91%)	3,179 (39.36%)	
Area of Residence[2]				
Urban	8,251 (75.51%)	2,119 (74.35%)	6,132 (75.92%)	0.245
Rural	2,672 (24.45%)	730 (25.61%)	1,942 (24.04%)	
Tumor Group				
Colorectal	2,195 (20.09%)	553 (19.40%)	1,642 (20.33%)	
Lung	2,164 (19.80%)	609 (21.37%)	1,555 (19.25%)	
Prostate	2,007 (18.37%)	541 (18.98%)	1,466 (18.15%)	
Head & Neck	1,657 (15.16%)	442 (15.51%)	1,215 (15.04%)	0.013*
Breast	949 (8.68%)	249 (8.74%)	700 (8.67%)	
Other	1,955 (17.89%)	456 (16.00%)	1,499 (18.56%)	
Presence of Bone Metastasis	2,785 (25.49%)	953 (33.44%)	1,897 (23.49%)	<0.001*
Treatment Received				
Chemotherapy	6,083 (55.67%)	1,624 (56.98%)	4,459 (55.21%)	0.105
Surgery	4,214 (38.57%)	948 (33.26%)	3,266 (40.44%)	<0.001*
Radiation	3,152 (28.85%)	834 (29.26%)	2,318 (28.70%)	0.584
Hormone Therapy	2,538 (24.65%)	711 (24.95%)	1,827 (22.62%)	0.012
Immunotherapy	462 (4.23%)	119 (4.18%)	343 (4.25%)	0.914
Year of Diagnosis				
2004-2008	3,140 (28.74%)	774 (27.16%)	2,366 (29.29%)	
2009-2013	4,097 (37.49%)	1,192 (41.82%)	2,905 (35.97%)	<0.001*
2014-2017	3,690 (33.77%)	884 (31.02%)	2,806 (34.74%)	
History of Mental Health Diagnoses				
Substance Dependence	750 (6.86%)	258 (9.05%)	492 (6.09%)	<0.001*
Anxiety Disorders	919 (8.41%)	279 (9.79%)	640 (7.92%)	0.002*
Depressive Disorders	1,016 (9.30%)	353 (12.39%)	663 (8.21%)	<0.001*

[1] As of 2019/07/22

[2] Missing data for n=4

[3] Long-term prescribing defined as receipt of a 90-day or greater supply of opioids with less than a 30-day gap in supply within a 180-day period or receipt of ≥10 opioid prescriptions over one year.

* Represents statistical significance given an alpha of 0.05

Table A1.8: Prescribed Morphine Equivalent Daily Dosage (MEDD) During Long-Term Prescribing

	All Recipients of Long-Term Prescribing	Recipients with Duration ≥90 & <180 days	Recipients with Duration ≥180 & <365 days	Recipients with Duration ≥365 days	*p-value*
N	2,521	818	823	880	
Mean MEDD over Prescribing Period	100.7 ± 119.67	90.9 ± 102.9	107.4 ± 129.8	103.7 ± 124.4	*0.013**
Dosage at Initiation of Long-Term Prescribing[1]	71.0 ± 128.9	69.3 ± 144.2	72.05 ± 127.1	71.4 ± 114.7	*0.905*
Final Dose at Discontinuation [2]	163.8 ± 293.5	147.0 ± 293.7	188.4 ± 326.9	156.4 ± 257.0	*0.012**
Mean Difference from Starting Dose (95% CI)	**94.0 (82, 105)**	**78.2 (57, 100)**	**118.8 (96, 141)**	**85.7 (68, 104)**	*0.015**
p-value for change in dosage	***<0.001****	***<0.001****	***<0.001****	***<0.001****	

[1] Missing data for n=2 due to inability to estimate dosage; [2] Missing data for n=52 due to inability to estimate dosage

Table A1.9: Multivariable Logistic Regression of Factors Associated with Early Onset of Long-Term Prescribing among Decedents (n= 2,091)

	Odds Ratio (OR)	95% Confidence Interval	p-value
Age at Diagnosis[1]	0.89	0.82, 0.97	0.006*
Survival Time (months)	1.03	1.02, 1.03	<0.001*
Year of Diagnosis[2]	1.05	1.02, 1.08	<0.001*
Sex			
Male	Reference		0.207
Female	1.16	0.92, 1.45	
Area of Residence[2]			
Rural	Reference		0.512
Urban	0.93	0.74, 1.16	
Tumor Group			
Lung	Reference		
Colorectal	0.97	0.70, 1.34	
Prostate	0.75	0.38, 1.48	0.030*
Head & Neck	1.37	0.93, 2.02	
Breast	1.43	0.77, 2.67	
Other	1.14	0.84, 1.56	
Presence of Bone Metastasis	1.72	1.33, 2.22	<0.001*
Treatment Received			
Chemotherapy	1.07	0.85, 1.34	0.587
Surgery	0.65	0.52, 0.82	<0.001*
Radiation	0.99	0.78, 1.25	0.911
Hormone Therapy	0.98	0.52, 1.84	0.941
Immunotherapy	1.19	0.72, 2.00	0.498
History of Mental Health Diagnoses[2]			
Substance Dependence	1.26	0.81, 1.96	0.306
Anxiety Disorders	0.90	0.65, 1.24	0.522
Depressive Disorders	1.16	0.87, 1.54	0.300
Neighborhood-level Income			
Lowest Quintile	Reference		
2nd Quintile	1.29	0.95, 1.75	0.405
3rd Quintile	1.10	0.80, 1.51	
4th Quintile	0.99	0.71, 1.38	
Highest Quintile	1.05	0.74, 1.49	
Neighbourhood-level Education			
Lowest Quintile	Reference		
2nd Quintile	0.72	0.54, 0.97	0.233
3rd Quintile	0.76	0.55, 1.04	
4th Quintile	0.81	0.58, 1.13	
Highest Quintile	0.87	0.60, 1.25	

[1] Age at diagnosis was considered as a continuous variable was scaled into years divided by 10.
[2] Year of diagnosis was considered as a continuous variable for number of years after 2000.
* Represents statistical significance given an alpha of 0.05

Table A1.10: Subgroup Analyses of Early Onset of Long-Term Prescribing by Sex and Tumor Site

Stratification Variable	Sex		Primary Tumour Site				
	Male	**Female**	**Lung**	**Colorectal**	**Prostate**	**Head/Neck**	**Breast**
N	**1,220**	**871**	**487**	**425**	**427**	**232**	**182**
Age at Diagnosis[1]	0.86* (0.77,0.96)	0.93 (0.82, 1.05)	0.78* (0.63, 0.96)	0.86 (0.72, 1.03)	0.93 (0.77, 1.13)	0.83 (0.62, 1.10)	1.01 (0.76, 1.35)
Survival Time (months)	1.02* (1.01, 1.03)	1.03* (1.03, 1.04)	1.05* (1.03, 1.06)	1.03* (1.02, 1.04)	1.01* (1.00, 1.02)	1.04* (1.02, 1.05)	1.02* (1.00, 1.03)
Year of Diagnosis[2]	1.05* (1.02, 1.09)	1.05* (1.00, 1.09)	1.06* (1.00, 1.12)	1.05 (0.98, 1.12)	1.00 (0.94, 1.07)	1.10* (1.00, 1.23)	1.02 (0.91, 1.15)
Sex							
Male	N/A	N/A	Reference	Reference	N/A	Reference	N/A
Female			1.50* (1.00, 2.26)	1.16 (0.75, 1.81)		1.09 (0.51, 2.31)	
Area of Residence[2]							
Rural	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Urban	0.92 (0.69, 1.22)	0.95 (0.66, 1.38)	0.72 (0.43, 1.20)	1.17 (0.69, 2.00)	1.12 (0.69, 1.85)	1.54 (0.70, 3.41)	1.00 (0.43, 2.26)
Tumor Group							
Lung	Reference	Reference	N/A	N/A	N/A	N/A	N/A
Colorectal	1.21 (0.77, 1.90)	0.81 (0.50, 1.30)					
Prostate	0.86 (0.26, 2.71)	N/A					
Head & Neck	1.64* (1.01, 2.69)	1.09 (0.54, 2.22)					
Breast	N/A	1.38 (0.66, 2.93)					
Other	1.47 (0.94, 2.32)	0.99 (0.63, 1.55)					
Presence of Bone Metastasis	1.65* (1.17, 2.33)	1.91* (1.28, 2.86)	1.72* (1.13, 2.61)	2.22 (0.79, 6.62)	2.45* (1.32, 4.71)	2.33 (0.51, 12.92)	2.86* (1.17, 7.20)
Treatment Received							
Chemotherapy	1.10 (0.80, 1.51)	1.01 (0.72, 1.43)	1.07 (0.68, 1.70)	1.12 (0.60. 2.11)	0.63 (0.26, 1.47)	1.48 (0.71, 3.08)	0.80 (0.34, 1.86)
Surgery	0.68* (0.50, 0.91)	0.63* (0.43, 0.90)	0.83 (0.24, 2.86)	0.41* (0.25, 0.65)	1.02 (0.56, 1.85)	0.76 (0.40, 1.45)	0.66 (0.32, 1.33)
Radiation	1.05 (0.76, 1.45)	0.95 (0.66, 1.37)	0.88 (0.56, 1.36)	1.72* (1.04, 2.86)	1.59 (0.67, 3.82)	0.89 (0.36, 2.20)	0.87 (0.26, 3.04)
Hormone Therapy	1.18 (0.38, 3.82)	0.76 (0.33, 1.70)	N/A	N/A	1.00 (0.31, 3.39)	N/A	0.72 (0.26, 1.91)
Immunotherapy	1.08 (0.55, 2.13)	1.45 (0.64, 3.38)	0.98 (0.20, 4.83)	1.01 (0.42, 2.34)	N/A	1.85 (0.38, 10.86)	1.17 (0.24, 6.87)
History of Mental Health Diagnoses[2]							
Substance Dependence	1.34 (0.79, 2.29)	0.94 (0.41, 2.14)	1.25 (0.54, 2.86)	2.62 (0.78, 9.64)	1.62 (0.53, 5.32)	0.77 (0.25, 2.33)	*Not calc. (n=2)*
Anxiety Disorders	0.80 (0.50, 1.27)	1.00 (0.63, 1.58)	0.92 (0.49, 1.73)	0.57 (0.24, 1.24)	1.07 (0.44, 2.59)	1.00 (0.36, 2.80)	1.23 (0.44, 3.76)
Depressive Disorders	1.20 (0.79, 1.82)	1.19 (0.80, 1.77)	0.77 (0.42, 1.38)	1.35 (0.67, 2.72)	1.89 (0.89, 4.14)	0.82 (0.34, 1.96)	1.71 (0.60, 5.28)

Neighborhood-level Income							
Lowest Quintile	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2nd Quintile	1.26 (0.84, 1.88)	1.35 (0.83, 2.20)	1.77 (0.94, 3.39)	1.03 (0.47, 2.23)	1.18 (0.59, 2.36)	1.60 (0.57, 4.67)	0.71 (0.21, 2.35)
3rd Quintile	0.98 (0.64, 1.50)	1.35 (0.82, 2.22)	1.32 (0.65, 2.69)	0.85 (0.40, 1.84)	0.73 (0.36, 1.49)	1.87 (0.65, 5.54)	1.46 (0.44, 4.95)
4th Quintile	1.00 (0.64, 1.54)	1.04 (0.62, 1.74)	1.09 (0.54, 2.19)	0.77 (0.35, 1.68)	0.96 (0.45, 2.04)	2.11 (0.66, 6.99)	1.08 (0.34, 3.40)
Highest Quintile	1.00 (0.63, 1.59)	1.19 (0.70, 2.06)	1.15 (0.55, 2.42)	0.63 (0.28, 1.43)	1.09 (0.48, 2.46)	2.34 (0.73, 7.88)	0.81 (0.23, 2.73)
Neighborhood-level Education							
Lowest Quintile	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2nd Quintile	0.72 (0.49, 1.05)	0.72 (0.44, 1.170	0.73 (0.37, 1.41)	1.12 (0.55, 2.28)	0.50* (0.26, 0.95)	0.25* (0.09, 0.68)	0.35 (0.10, 1.13)
3rd Quintile	0.66* (0.44, 0.99)	0.91 (0.55, 1.51)	1.20 (0.60, 2.39)	0.81 (0.38, 1.76)	0.53 (0.26, 1.05)	0.46 (0.16, 1.29)	0.31 (0.09, 1.04)
4th Quintile	0.74 (0.48, 1.13)	0.92 (0.54, 1.58)	1.10 (0.53, 2.32)	0.93 (0.42, 2.10)	0.52 (0.25, 1.08)	0.49 (0.16, 1.46)	0.49 (0.12, 1.82)
Highest Quintile	0.82 (0.51, 1.33)	0.93 (0.52, 1.66)	1.43 (0.64, 3.24)	1.34 (0.57, 3.15)	0.59 (0.25, 1.41)	0.26* (0.07, 0.89)	0.34 (0.08, 1.38)

[1] Age at diagnosis was considered as a continuous variable and was scaled into years divided by 10.

[2] Year of diagnosis was considered as a continuous variable for number of years after 2000.

* Represents statistical significance given an alpha of 0.05

Table A1.11: Association of Long-Term Prescribing Practices with Opioid-Related Encounters

	N	Long-Term Recipients Experiencing an Opioid-Related Encounter (N)	p-value	Incidence Rate (per 100 person-years) [95% CI]	p-value from the IRR
Duration of Prescribing Period			**<0.001***		
≤9 months	1,321	27 (2.04%)		2.21 [1.52, 3.10]	0.648
>9 months	1,200	58 (4.83%)		2.44 [1.89, 3.09]	
High Dosage (>100mg mean MEDD)			**<0.001***		
Yes	816	45 (5.51%)		4.79 [3.65, 6.18]	**<0.001***
No	1,705	40 (2.35%)		1.38 [0.99, 1.86]	
Combined Dosage/ Duration					
High Dose & >9months	412	31 (7.52%)		4.51 [3.21, 6.17]	
High Dose & ≤9 months	404	14 (3.46%)	**<0.001***	5.46 [3.34, 8.43]	0.486
Low Dose & >9 months	788	27 (3.43%)		1.51 [1.01, 2.16]	
Low Dose & ≤9 months	917	13 (1.42%)		1.15 [0.61, 1.97]	0.493
Early Onset					
Yes	989	48 (4.85%)	**0.007***	2.79 [2.13, 3.58]	**0.010***
No	1,102	29 (2.63%)		4.98 [3.40, 7.02]	
Concurrent Medications[1]					
NSAIDs					
Yes	698	30 (4.30%)	0.111	2.32 [1.60, 3.26]	0.927
No	1,823	55 (3.02%)		2.37 [1.84, 3.01]	
Anxiolytics					
Yes	850	43 (5.06%)	**<0.001***	3.36 [2.51, 4.39]	**0.001***
No	1,671	42 (2.51%)		1.77 [1.31, 2.35]	
Benzodiazepines					
Yes	1,195	52 (4.35%)	**0.010***	3.15 [2.42, 4.02]	**0.001***
No	1,326	33 (2.49%)		1.64 [1.16, 2.27]	
Antidepressants					
Yes	996	48 (4.82%)	**0.001***	2.94 [2.22, 3.81]	**0.027***
No	1,525	37 (2.43%)		1.89 [1.38, 2.53]	
Neuroleptics					
Yes	990	48 (4.85%)	**0.001***	3.90 [2.97, 5.01]	**<0.001***
No	1,531	37 (2.42%)		1.49 [1.07, 2.03]	

[1] Prescriptions classified according to ATC code *(Table S2)* and defined based on having any prescriptions filled during the period of long-term opioid prescribing.

Table A1.12: Sensitivity Analyses for Categorization of Dosage Level, Duration, & Early Onset

Categorization of Continuous Variables	N	Long-term Recipients Experiencing an Opioid-Related Encounter (n)	p-value	Incidence Rate (per 100 person-years) [95% CI]	p-value
Length of Prescribing Period					
≤6 months >6 months	846 1,675	15 (1.77%) 70 (4.18%)	0.002*	1.60 [0.90, 2.64] 2.56 [2.06, 3.17]	0.080
≤9 months **>9 months**	**1,321** **1,200**	**27 (2.04%)** **58 (4.83%)**	**<0.001***	**2.21 [1.52, 3.10]** **2.44 [1.89, 3.09]**	**0.648**
≤1 year >1 year	1,645 876	37 (2.24%) 48 (5.45%)	<0.001*	2.23 [1.62, 3.01] 2.46 [1.87, 3.18]	0.640
≤18 months >18 months	2,028 493	52 (2.56%) 33 (6.69%)	<0.001*	2.25 [1.70, 2.90] 2.53 [1.83, 3.41]	0.554
≤2 years >2 years	2,217 304	63 (2.84%) 22 (7.24%)	<0.001*	2.49 [1.96, 3.12] 2.05 [1.34, 3.00]	0.397
High Dosage					
≤50mg mean MEDD >50mg mean MEDD	1,013 1,508	15 (1.48%) 70 (4.64%)	<0.001*	0.80 [0.46, 1.31] 3.71 [2.96, 4.58]	<0.001*
≤75mg mean MEDD >75mg mean MEDD	1,423 1,098	28 (1.97%) 57 (5.19%)	<0.001*	1.10 [0.74, 1.58] 4.37 [3.42, 5.50]	<0.001*
≤100mg mean MEDD **>100mg mean MEDD**	**1,705** **816**	**40 (2.35%)** **45 (5.51%)**	**<0.001***	**1.38 [0.99, 1.86]** **4.79 [3.65, 6.18]**	**<0.001***
≤150mg mean MEDD >150mg mean MEDD	2,034 487	56 (2.75%) 29 (5.95%)	<0.001*	1.78 [1.37, 2.27] 5.15 [3.64, 7.06]	<0.001*
≤200mg mean MEDD >200mg mean MEDD	2,183 338	63 (2.89%) 22 (6.51%)	<0.001*	1.85 [1.44, 2.34] 6.16 [4.19, 8.75]	<0.001*
Time from Onset of Long-Term Prescribing to Death (n= 2,091 decedents)					
≤6 months >6 months	467 1,624	8 (1.71%) 69 (4.25%	0.010*	4.44 [1.92, 8.75] 3.20 [2.56, 3.96]	0.376
≤9 months >9 months	822 1,269	19 (2.31%) 58 (4.57%)	0.007*	5.53 [3.47, 8.38] 2.92 [2.28, 3.68]	0.013*
≤1 year **>1 year**	**1,102** **989**	**29 (2.63%)** **48 (4.85%)**	**0.007***	**4.98 [3.40, 7.02]** **2.79 [2.13, 3.58]**	**0.010***
≤18 months >18 months	1,509 582	44 (2.91%) 33 (5.67%)	0.003*	4.13 [3.03, 5.49] 2.72 [1.99, 3.62]	0.044*
≤2 years >2 years	1,702 389	52 (3.05%) 25 (6.43%)	0.001*	3.94 [2.99, 5.09] 2.58 [1.79, 3.58]	0.046*

Appendix 2: Supplementary Tables for Chapter 4

Table A2.1: Univariate Analysis of Association between NMOU Behaviours and Patient Characteristics including Patients with Overuse Reported as Accidental

	Patients with NMOU	Patients without NMOU	p-value
N	20	26	
Age at Diagnosis	52.5 ± 11.7	65.3 ± 10.6	<0.001*
Sex			0.607
Male	14 (70%)	18 (69%)	
Female	6 (30%)	8 (31%)	
Primary Cancer Type			0.079
Head & Neck	9 (45%)	4 (15%)	
Lung	3 (15%)	8 (31%)	
Prostate	1 (5%)	7 (27%)	
Colorectal	4 (20%)	2 (8%)	
Breast	1 (5%)	2 (8%)	
Gastroesophageal	2 (10%)	1 (4%)	
Bladder	0 (0%)	1 (4%)	
Kidney	0 (0%)	1 (4%)	
Birth Country			0.416
Canada	15 (75%)	15 (58%)	
Other	2 (10%)	5 (19%)	
Marital Status			0.007*
Married	6 (30%)	19 (73%)	
Divorced, Widowed or Single	14 (70%)	7 (27%)	
Smoking Status			0.087
Lifetime Nonsmoker	3 (15%)	5 (19%)	
Former Smoker	7 (35%)	16 (62%)	
Current Smoker	10 (50%)	5 (19%)	
Smoking Exposure Level			0.388
Never Smokers (0 pack-years)	3 (15%)	5 (19%)	
Light Smokers (1-20 pack-years)	7 (35%)	9 (35%)	
Moderate Smokers (20-40 pack-years)	6 (30%)	2 (8%)	
Heavy Smokers (>40 pack-years)	4 (20%)	7 (27%)	
History of Alcohol Abuse			0.036*
Reported	12 (60%)	7 (27%)	
Not reported	8 (40%)	19 (73%)	
History of Recreational Drug Use			0.014*
Reported	7 (35%)	1 (4%)	
Not reported	13 (65%)	25 (96%)	
Limited Social Support			0.008*
Reported	13 (65%)	6 (23%)	
Not reported	7 (35%)	19 (73%)	
History of Mental Illness			0.016*
Reported	14 (70%)	8 (31%)	
Not reported	6 (30%)	18 (69%)	
Pain Etiology			0.387
Cancer-related pain	10 (50%)	17 (65%)	
Non-cancer pain	1 (5%)	4 (15%)	
Mixed	6 (30%)	5 (19%)	
Neuropathic Component			0.038*
Reported	5 (25%)	15 (58%)	
Not reported	15 (75%)	11 (42%)	

Appendix 3: Permissions from Publisher and Co-Authors for Paper 1

A3.1 Publisher Copyright Agreement

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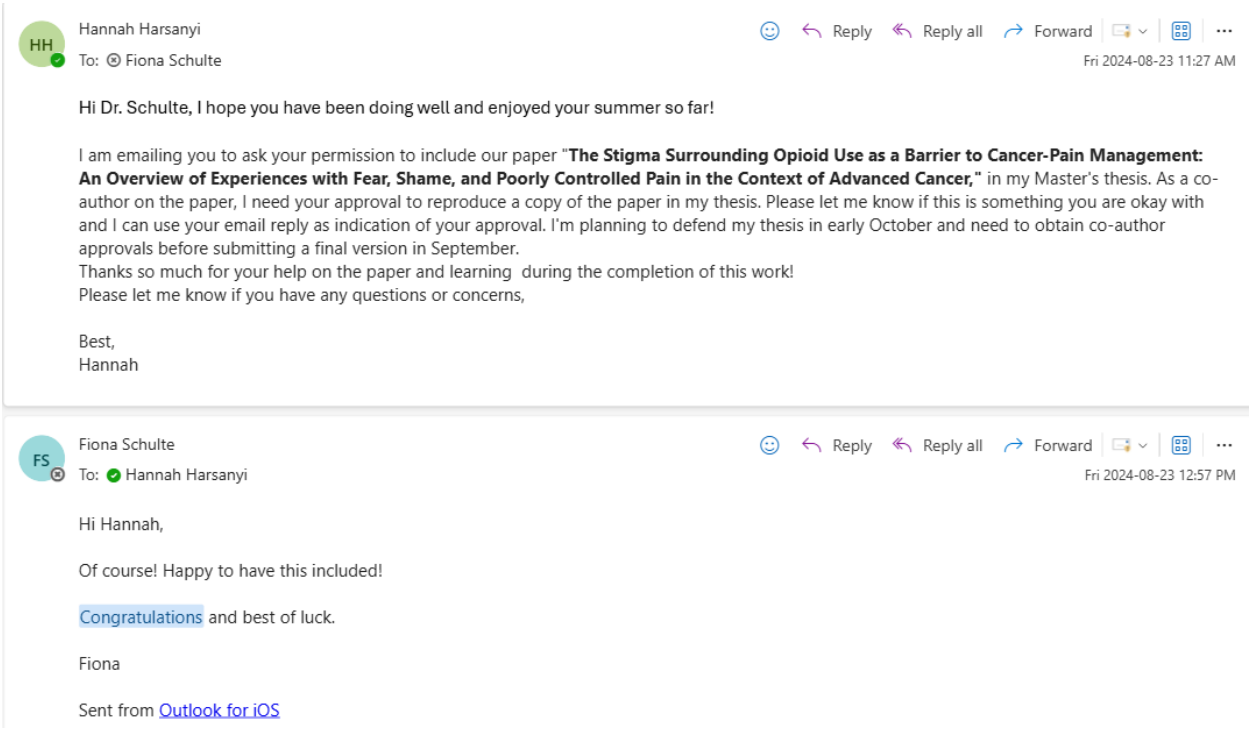

Hannah Harsanyi
To: Fiona Schulte
Reply | Reply all | Forward
Fri 2024-08-23 11:27 AM

Hi Dr. Schulte, I hope you have been doing well and enjoyed your summer so far!

I am emailing you to ask your permission to include our paper "**The Stigma Surrounding Opioid Use as a Barrier to Cancer-Pain Management: An Overview of Experiences with Fear, Shame, and Poorly Controlled Pain in the Context of Advanced Cancer,**" in my Master's thesis. As a co-author on the paper, I need your approval to reproduce a copy of the paper in my thesis. Please let me know if this is something you are okay with and I can use your email reply as indication of your approval. I'm planning to defend my thesis in early October and need to obtain co-author approvals before submitting a final version in September.
Thanks so much for your help on the paper and learning during the completion of this work!
Please let me know if you have any questions or concerns,

Best,
Hannah

Fiona Schulte
To: Hannah Harsanyi
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Hi Hannah,

Of course! Happy to have this included!

Congratulations and best of luck.

Fiona

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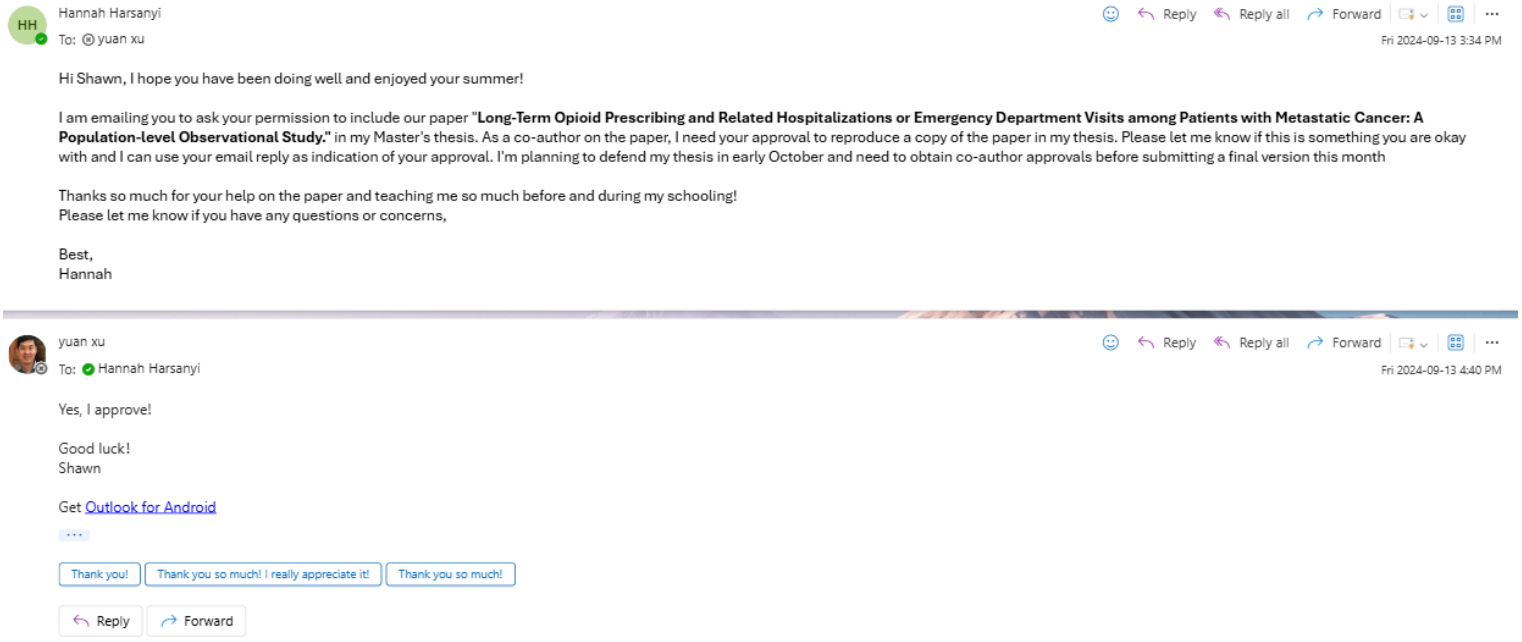

Hannah Harsanyi
To: yuan xu

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Hi Shawn, I hope you have been doing well and enjoyed your summer!

I am emailing you to ask your permission to include our paper "**Long-Term Opioid Prescribing and Related Hospitalizations or Emergency Department Visits among Patients with Metastatic Cancer: A Population-level Observational Study.**" in my Master's thesis. As a co-author on the paper, I need your approval to reproduce a copy of the paper in my thesis. Please let me know if this is something you are okay with and I can use your email reply as indication of your approval. I'm planning to defend my thesis in early October and need to obtain co-author approvals before submitting a final version this month

Thanks so much for your help on the paper and teaching me so much before and during my schooling!
Please let me know if you have any questions or concerns,

Best,
Hannah

yuan xu
To: Hannah Harsanyi

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Yes, I approve!

Good luck!
Shawn

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